

Follow-up and (very) long term outcomes of our preterm infants

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Plan

- Follow-Up of Preterm Infants in Belgium**
- 5 years outcomes @Liege**
- What about school age ?**
- Beyond infancy...**

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Royal decree 2014

- Convention between Belgian health insurance system (INAMI) and several specialized centres.
- First convention dedicated to prevention in the paediatrics population.

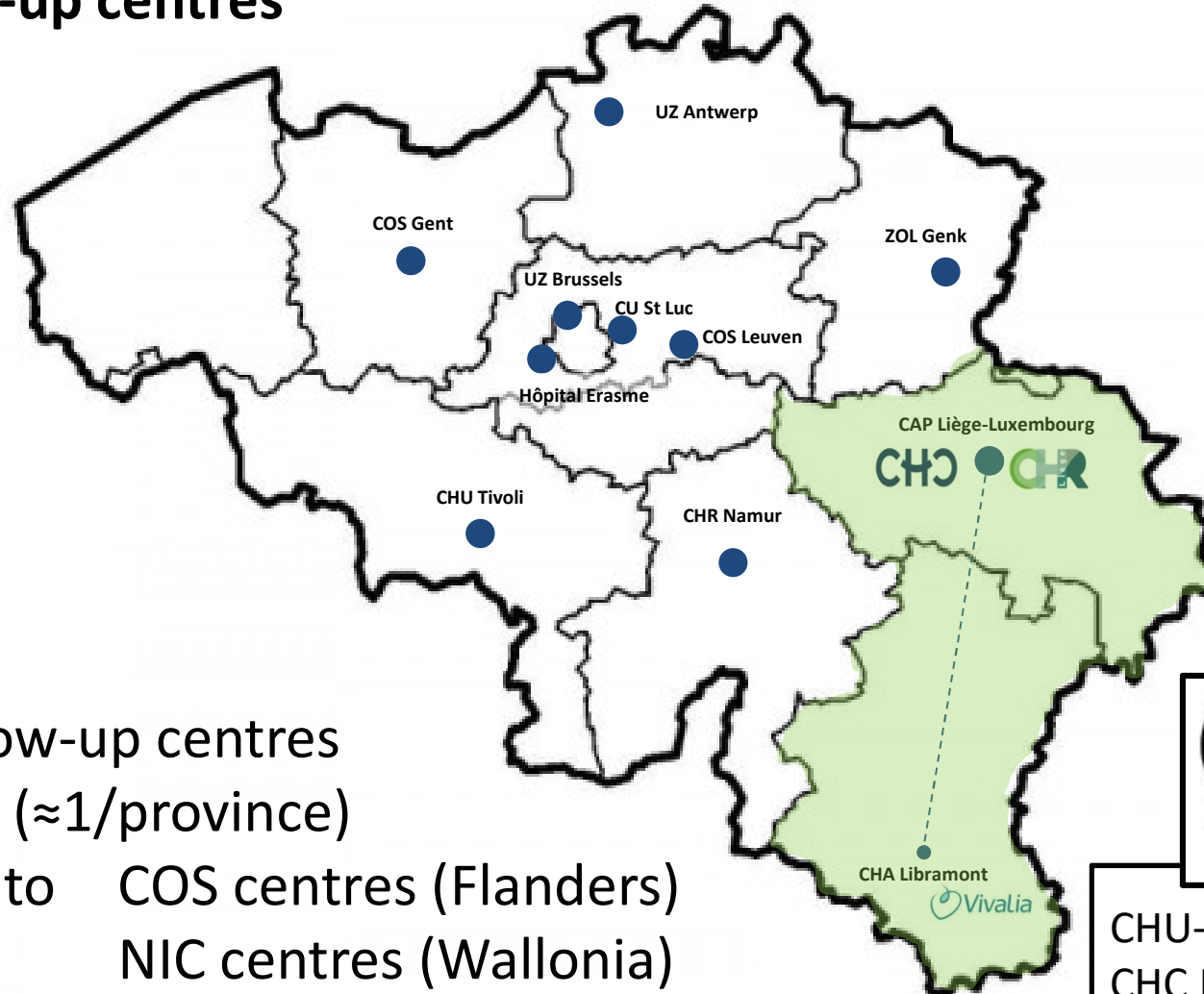
Follow-up convention

- Preterm infants <32wks GA and/or <1500g
- Multidisciplinary standardised national assessment
- 4 different ages
 - 3-6 months CA, 9-14 months CA, 22-26 months CA, 4.5-5.5 years
- Funding 1.265€/infant
- Refers patients for rehabilitation and/or specialised medical cares

Data collection

- Prospective recording of follow-up outcomes

Follow-up centres



10 follow-up centres
(≈ 1 /province)

Linked to COS centres (Flanders)
NIC centres (Wallonia)



CHU-CHR Liège
CHC Mont Legia
CHA Libramont

Multidisciplinary standardised national assessment

3-6 months CA	9-14 months	22-26 months	4.5-5.5 years
Physiotherapist <i>AIMS</i>	Physiotherapist <i>AIMS, Bayley III</i>	Physiotherapist <i>Bayley III</i>	Physiotherapist <i>M-ABC 2</i>
Psychologist <i>EPDS</i>	Psychologist <i>Bayley III</i>	Psychologist <i>Bayley III</i>	Neuropsychologist <i>WPPSI (and more)</i>
Social worker	Social worker	Social worker	Speech therapist <i>Language and preschool skills</i>
Neonatologist/ Child neurologist	Neonatologist/ Child neurologist	Neonatologist/ Child neurologist	Social worker
			Neonatologist/ Child neurologist

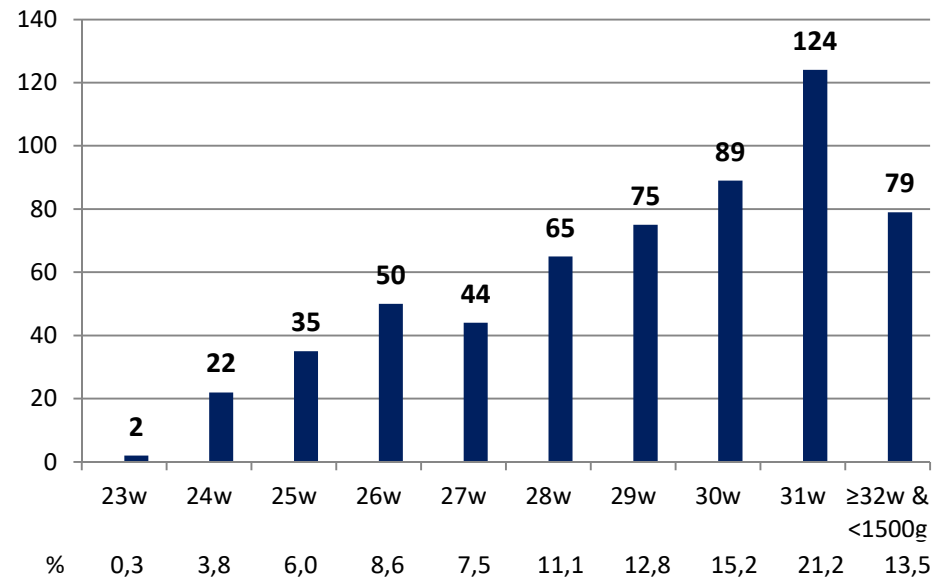
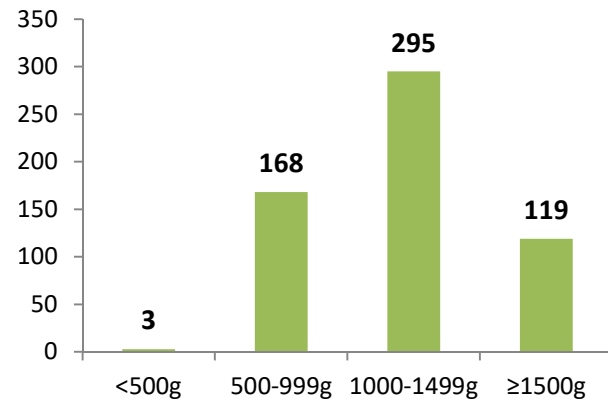
Additional medical assessment may be required.
 Visit @3.5-4 years systematically organized for evaluation of language abilities.

Plan

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POPULATION

- Years 2012 – 2013 – 2014
- Preterm newborn admitted to
 CHU-CHR Liège = 330
 CHC Liège = 255
Total = 585 patients



Preterm births

(n = 585)

n(%) / mean ± SD

Perinatal characteristics

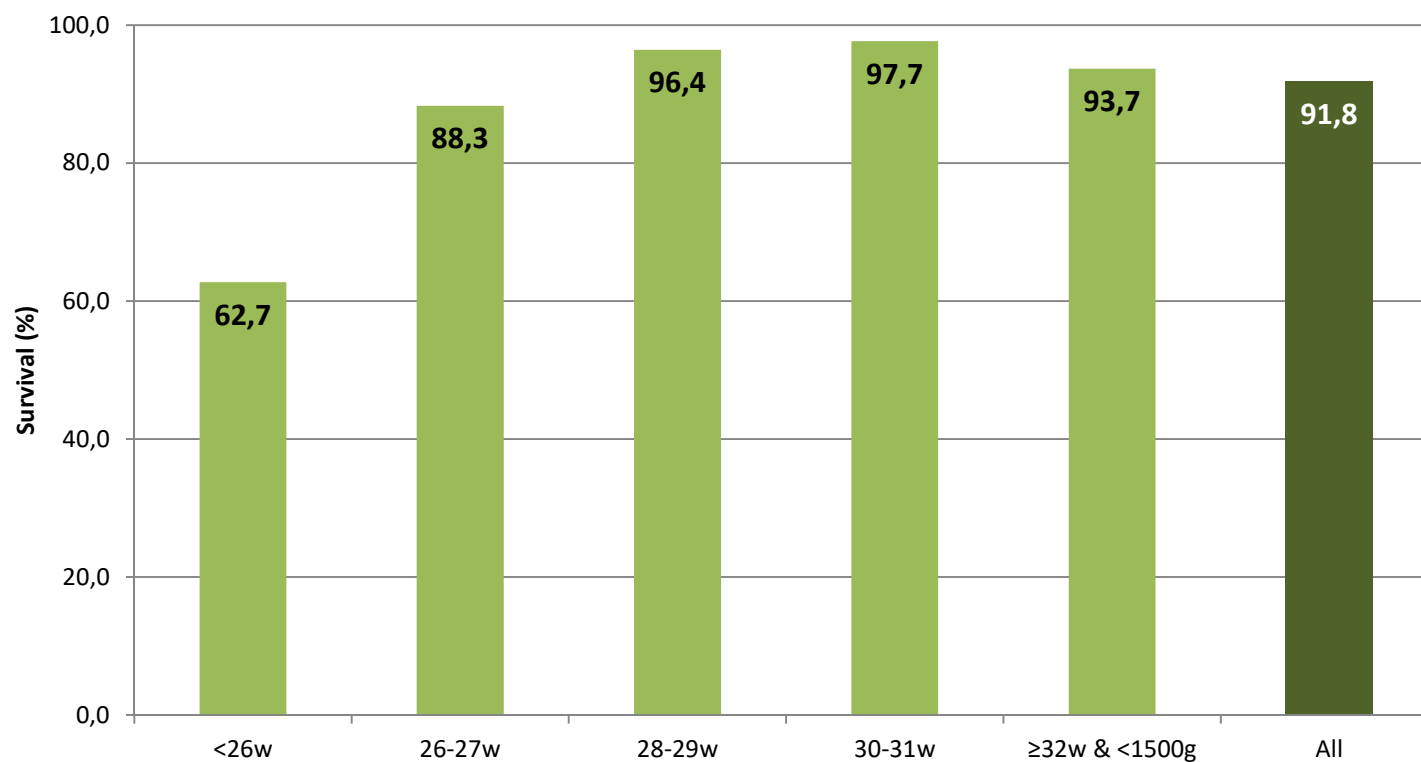
GA (weeks)	29.2 ± 2.6
BW (g)	1231 ± 359
Gender (male)	325 (55.6)
Multiple birth	182 (31.1)
Apgar @5min	7.9 ± 1.6
Antenatal CS	376 (64.3)

Therapies and morbidities

Surfactant	294 (50.2)
BDP @36w	36 (6.1)
Systemic corticotherapy	46 (7.9)
NEC	27 (7.4)
IVH	
grade I-II	53 (9.1)
grade III-IV	24 (4.1)
PVL	
grade I-II	38 (6.5)
grade III-IV	2 (0.3)
ROP (all grades)	34 (6.9)

SURVIVAL

- Global survival rate to NICU discharge : 91.8% (n=537)
- Highest mortality rates associated with lowest gestational ages



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- Global survival rate to NICU discharge : 91.8% (n=537)
- Highest mortality rates associated with lowest gestational ages

	Death before NICU discharge (n = 48) <i>n(%) / mean±SD</i>	Survival to NICU discharge (n= 537) <i>n(%) / mean±SD</i>	p-value
Perinatal characteristics			
GA (weeks)	26.9 ± 3.36	29.4 ± 2.46	<0.001
BW (g)	928 ± 353	1248 ± 348	<0.001
Gender (male)	30 (62.5)	295 (54.9)	0.31
Multiple birth	20 (41.6)	162 (30.2)	0.09
Apgar @5min	6.9 ± 1.2	8.0 ± 1.6	<0.001
Antenatal CS	20 (41.6)	356 (66.3)	0.001
Therapies and morbidities			
BDP @36w	1 (2.0)	35(6.5)	0.22
IVH			
grade I-II	9 (18.7)	44 (8.2)	0.01
grade III-IV	15 (31.2)	9 (1.7)	<0.001
PVL			
grade I-II	8 (16.6)	30 (5.6)	0.002
grade III-IV	1 (2)	1 (0.1)	0.03

FOLLOW-UP RATE

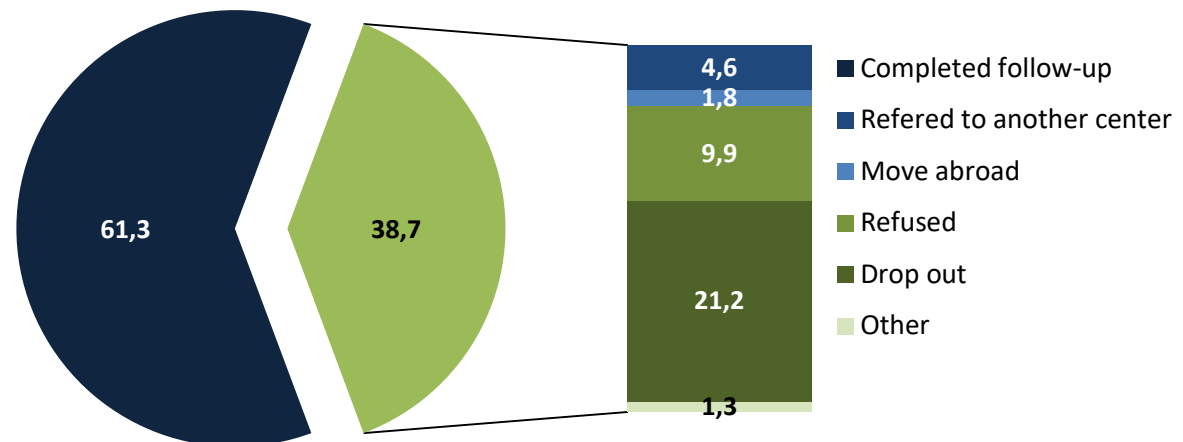
- Follow-up rate @5 years : 329/537 patients (61.3%)

Epipage (1997) : 77%

Epicture 2 (2006) : 55.3% (+18.3% from local records) @3 years

Swiss cohort(2006) : 81%

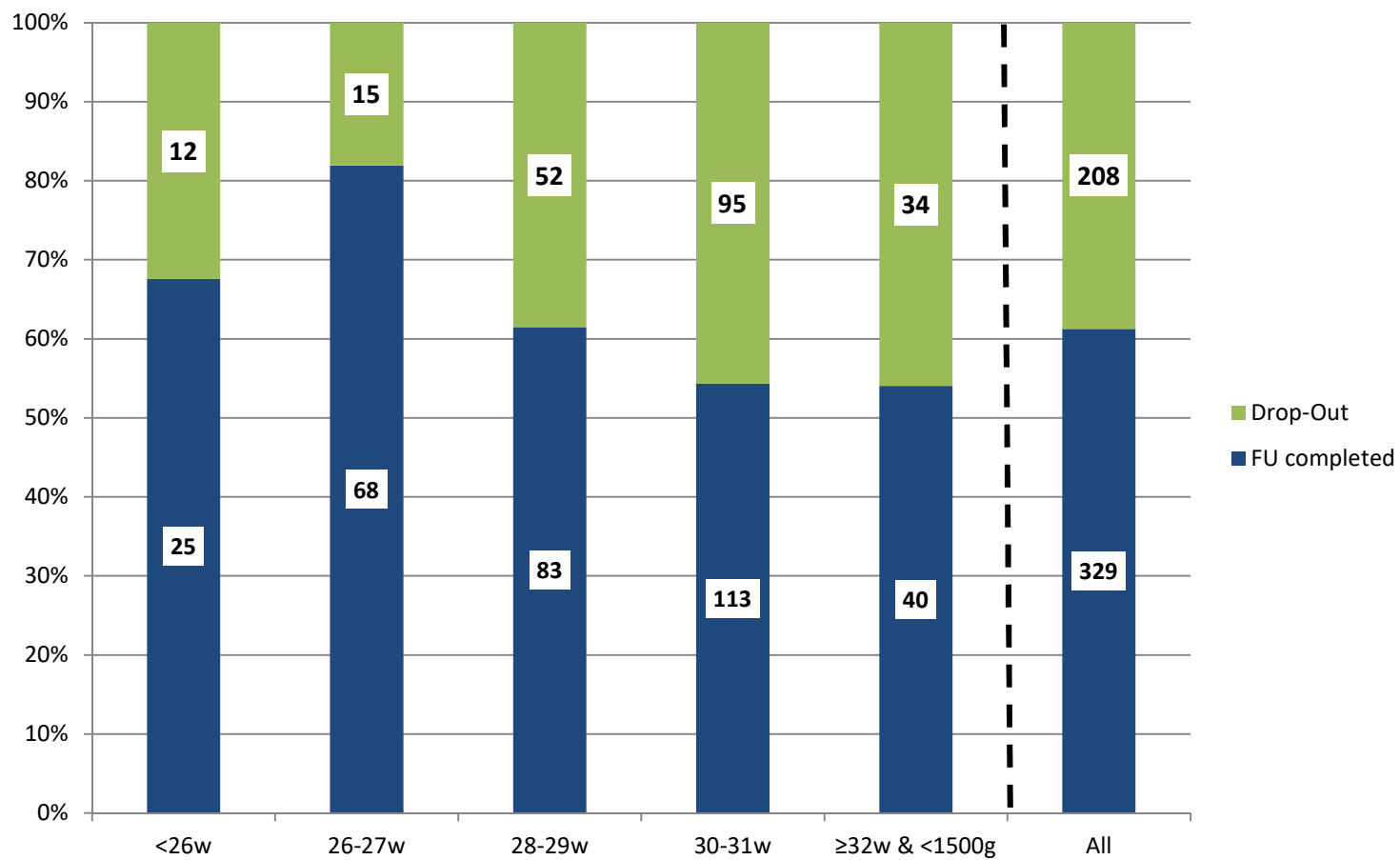
Lost to follow-up / reasons (%)









FOLLOW-UP RATE

	Lost to follow-up (n = 208) <i>n(%) / mean ± SD</i>	Follow-up completed (n = 329) <i>n(%) / mean ± SD</i>	p-value
Perinatal characteristics			
GA (weeks)	29.9 ± 2.37	29.1 ± 2.46	<0.001
BW (g)	1322 ± 330	1217 ± 353	<0.001
Gender (male)	114 (54.8)	181 (55.0)	0.96
Multiple birth	73 (35.1)	89 (27.0)	<0.05
Apgar @5min	8.2 ± 1.5	7.9 ± 1.7	0.10
Antenatal CS	122 (58.6)	234 (71.1)	<0.005
Therapies and morbidities			
BDP @36w	5 (2.4)	30 (10.0)	<0.005
IVH			
grade I-II	14 (6.7)	30 (9.1)	0.32
grade III-IV	3 (1.4)	6 (1.8)	0.73
PVL			
grade I-II	5 (2.4)	25 (7.6)	0.01
grade III-IV	0 (-)	1 (0.3)	0.42

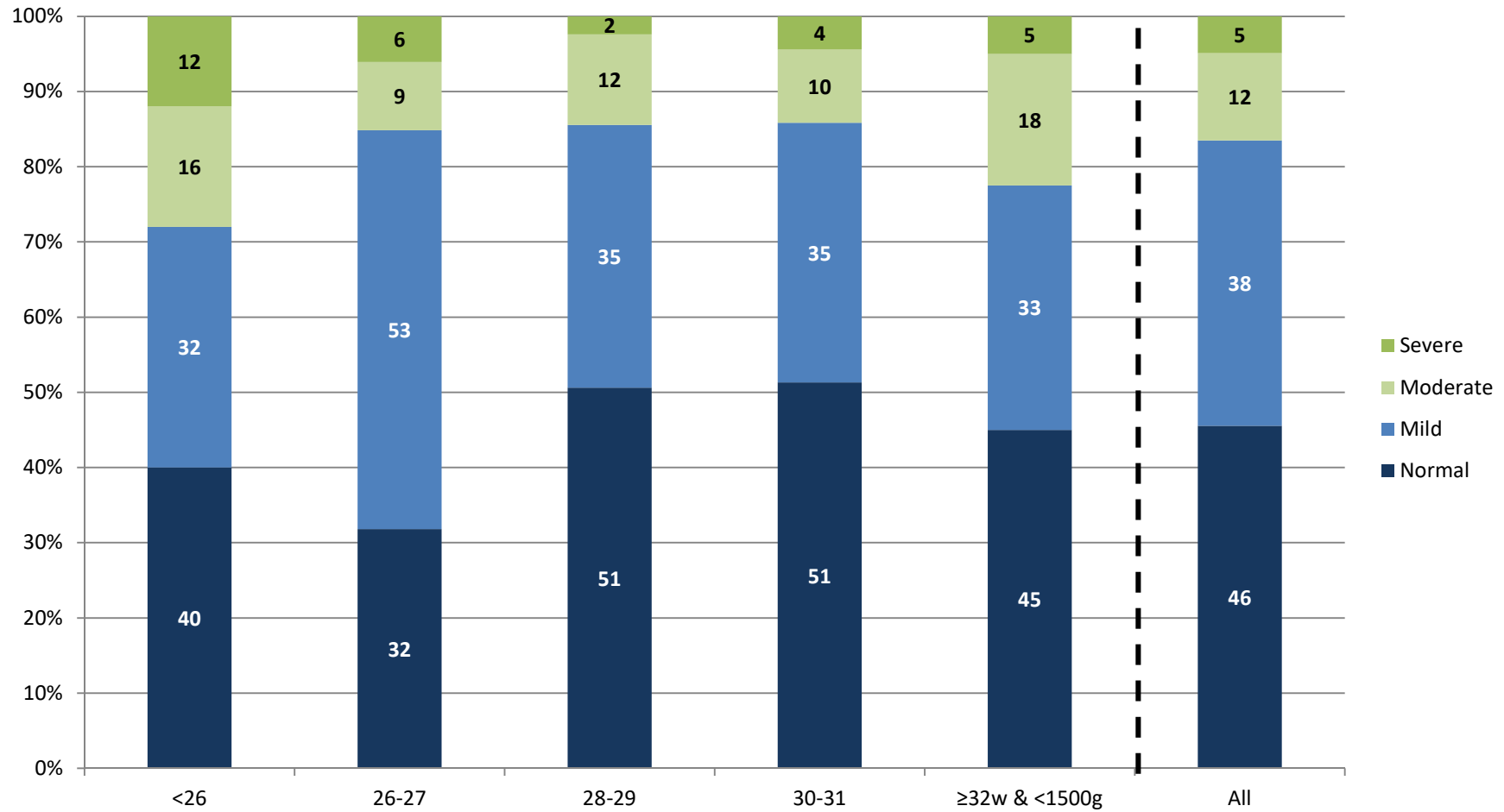
FOLLOW-UP RATE









NEURODEVELOPMENTAL OUTCOMES

	Normal outcome		
	Mild disability	Moderate disability	Severe disability
	CP – GMFCS I Motor Score (m-ABC) p5-15	CP – GMFCS II Motor Score (m-ABC) ≤p5	CP – GMFCS III-V
	IQ 70-84	IQ 50-69	IQ <50
	Mild behavioural problems (less than minor impairment in social functioning)	Moderate behavioural problems (impairment between mild and severe in social functioning)	Severe behavioural problems (results in marked impairment in social functioning)
	Mild language delay (<-1SD >-2SD)	Moderate language delay (<-2SD >-3SD)	Severe language delay (<-3SD)
	Hearing loss at <40dB	Hearing loss corrected at 40-70dB or not corrected at 70-90dB	No useful hearing
	Visual impairment with useful vision	Moderate reduced vision or unilateral blindness	Blind/Perceive lights

NEURODEVELOPMENTAL OUTCOMES



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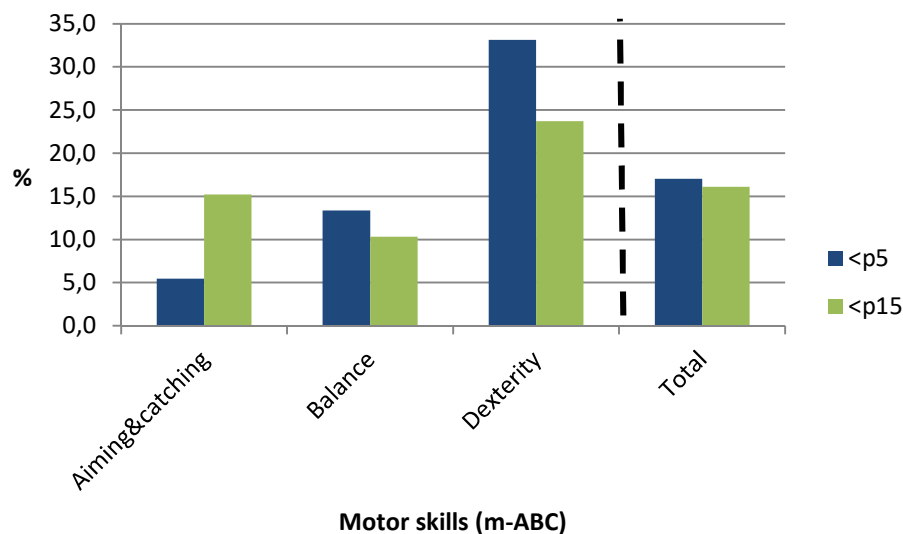
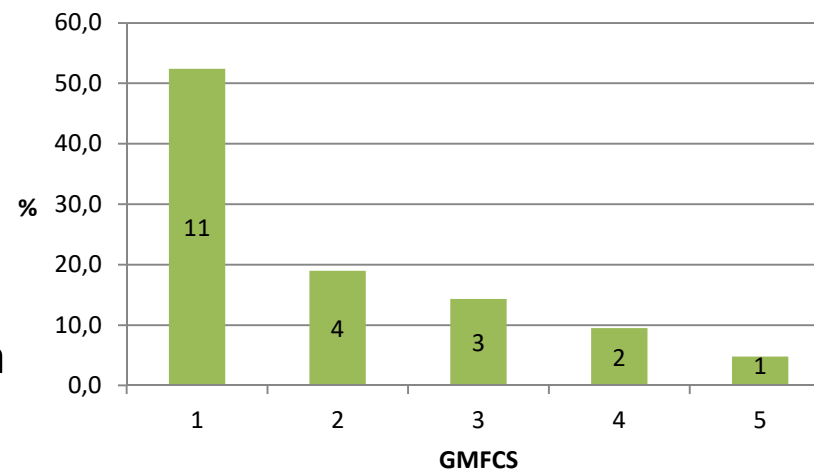
Normal outcome						
	Mild disability	%	Moderate disability	%	Severe disability	%
	CP – GMFCS I Motor Score (m-ABC) p5-15	3,3 11,3	CP – GMFCS II Motor Score (m-ABC) ≤p5	1,2 5,6	CP – GMFCS III-V	1,8
	IQ 70-84	8,6	IQ 50-69	3,1	IQ <50	3,1
	Mild behavioural problems (less than minor impairment in social functioning)	19,2	Moderate behavioural problems (between mild and severe)	7,4	Severe behavioural problems (marked impairment in social functioning)	1,8
	Mild language delay (<-1SD >-2SD)	23,3	Moderate language delay (<-2SD >-3SD)	8,2	Severe language delay (<-3SD)	4,9
	Hearing loss at <40dB	-	Hearing loss corrected 40- 70dB / not corrected 70-90dB	0,3	No useful hearing	-
	Visual impairment with useful vision	2,7	Moderate reduced vision or unilateral blindness	1,9	Blind/Perceive lights	0,3

MOTOR DISABILITIES

Cerebral palsy : 21 patients (6.3%)

Spastic 19 - Ataxic 1 - Other 1

↳ 43% bilateral and 57% unilateral
63% diplegia / 37% quadriplegia



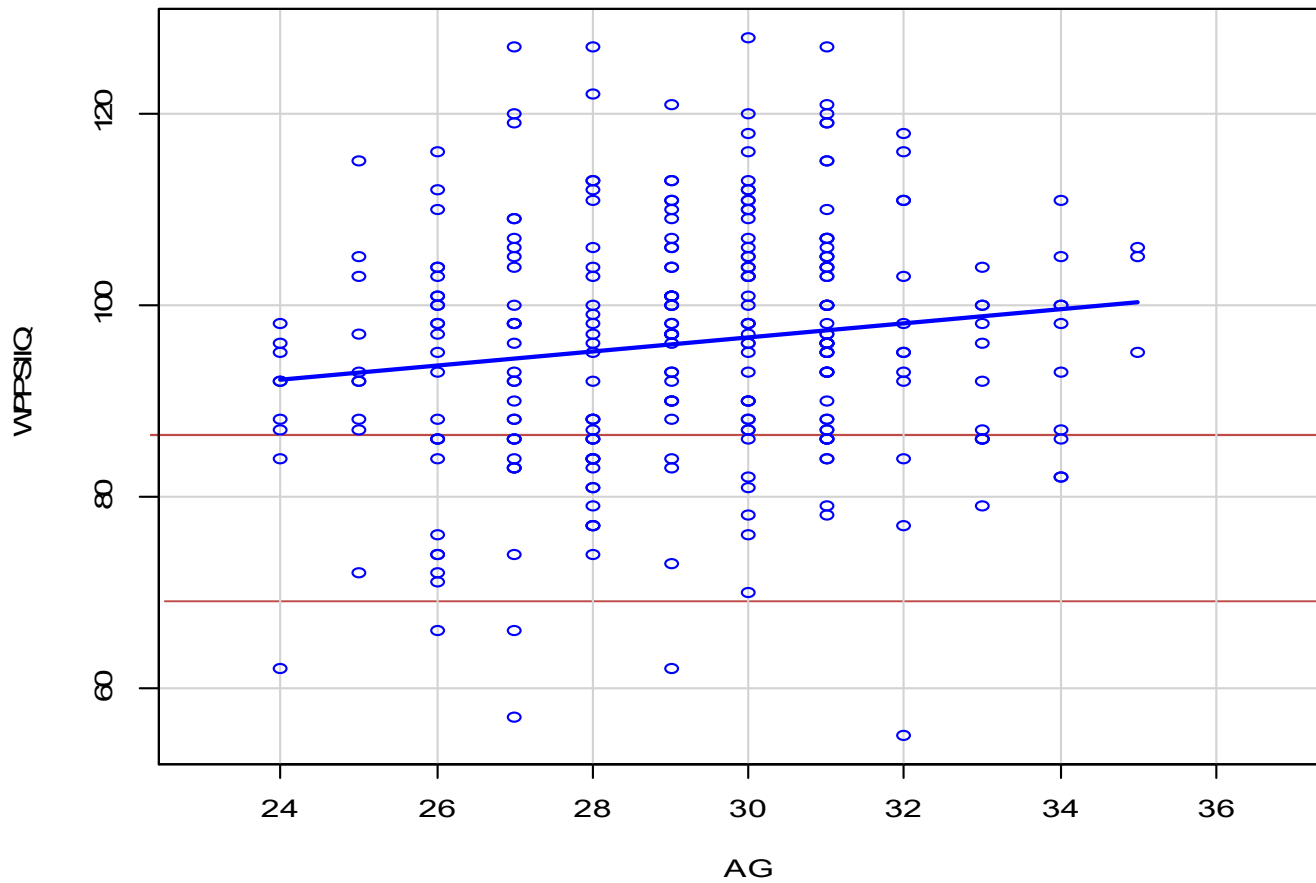
Among CP, 17% and 16% of preterm infants have motor skills fragilities or difficulties.

Dexterity is the most affected area.

COGNITIVE IMPAIRMENT

	<26 wk	26-27 wk	28-29 wk	30-31 wk	≥32 wk & <1500g	All	p-value
Total IQ (mean ± SD)	91.5 ± 11	93.2 ± 14	95.9 ± 12	99.1 ± 11	94.9 ± 12	96.1 ± 12	<0.05
Range IQ n (%)							
>85	16 (80.0)	42 (76.3)	58 (78.4)	89 (89.0)	31 (83.8)	239 (82.4)	0.12
70-84	2 (10.0)	11 (18.6)	15 (20.3)	9 (9.0)	5 (13.5)	42 (14.5)	
50-69	1 (5.0)	3 (5.1)	1 (1.4)	0 (0)	1 (2.7)	6 (2.1)	
<50	1 (5.0)	0 (0)	0 (0)	2 (2.0)	0 (0)	3 (1.0)	
Verbal comprehension	98 ± 12	97 ± 15	101 ± 15	104 ± 13	97 ± 13	101 ± 14	0.02
Working memory	96 ± 9	96 ± 12	97 ± 13	100 ± 9	101 ± 9	99 ± 11	0.10
Fluid reasoning	95 ± 9	94 ± 14	96 ± 9	98 ± 9	94 ± 9	96 ± 10	0.26
Visuospatial	89 ± 14	90 ± 16	92 ± 13	95 ± 13	92 ± 9	92 ± 13	0.10
Speed processing	89 ± 10	87 ± 9	90 ± 10	92 ± 13	91 ± 9	90 ± 11	0.26

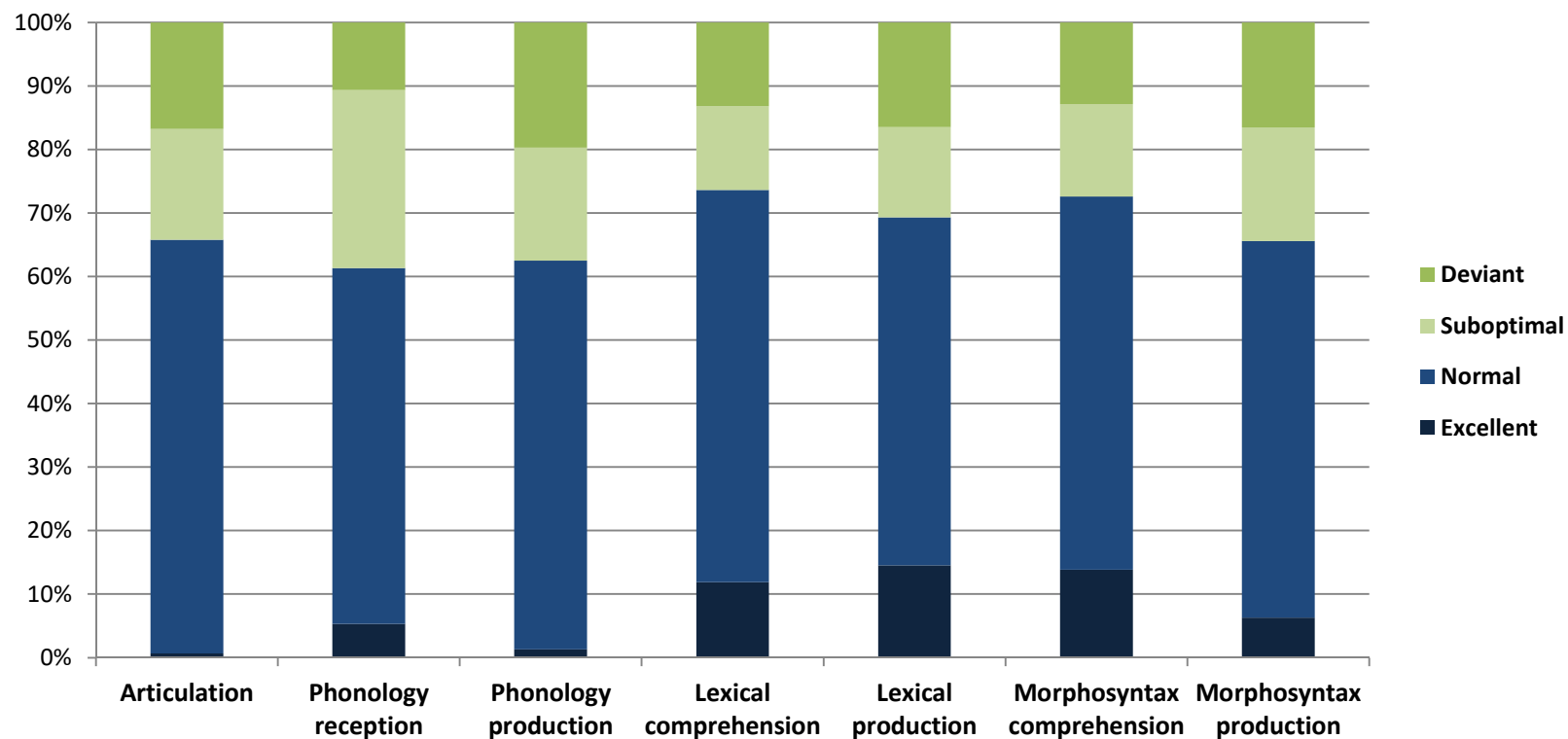
COGNITIVE IMPAIRMENT



R²=0.016
p=0.018

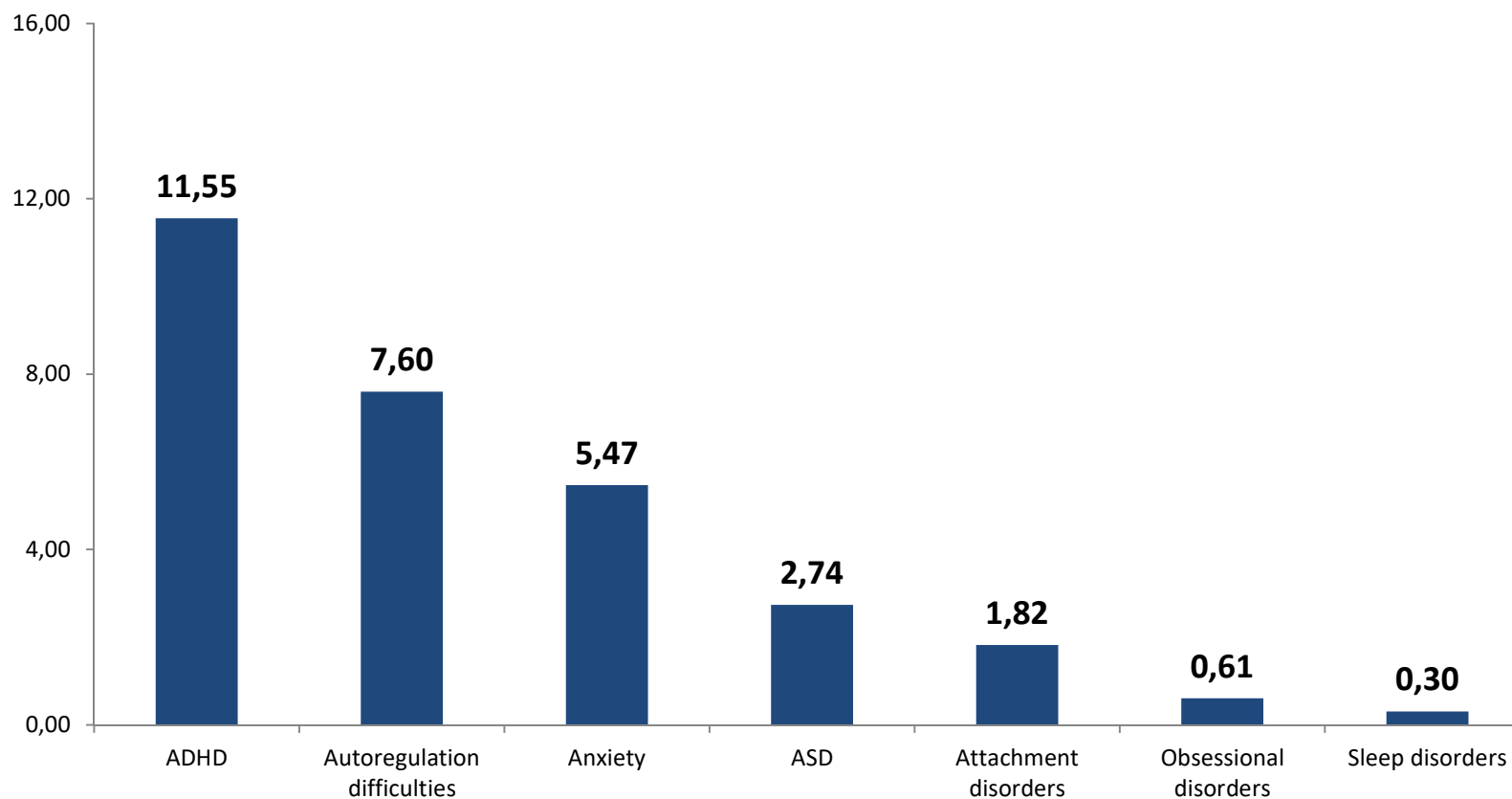
LANGUAGE

Articulation and phonology are more frequently impacted than lexical or morphosyntax areas, which can further lead to difficulties in written language.



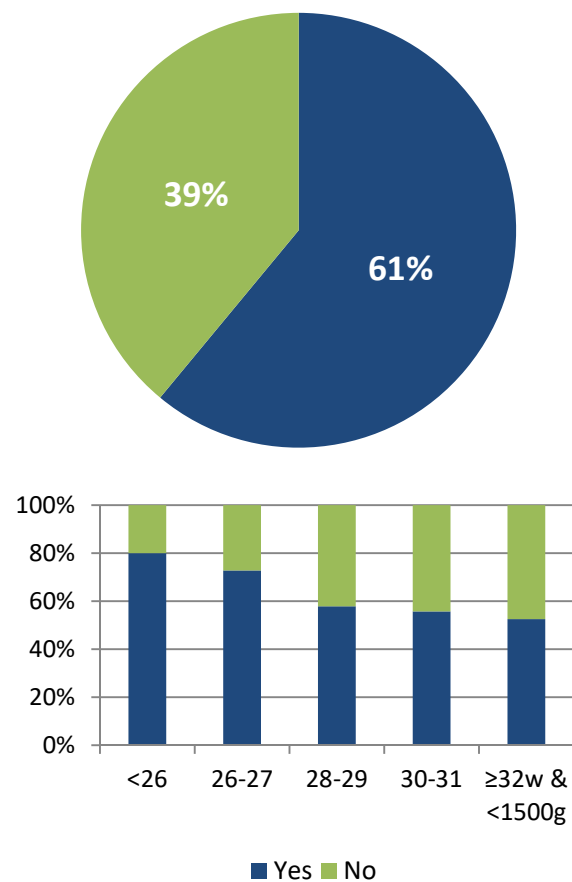
BEHAVIOR

30.4% of infants suffer from diagnosed/suspected behavioral problems at 5 years

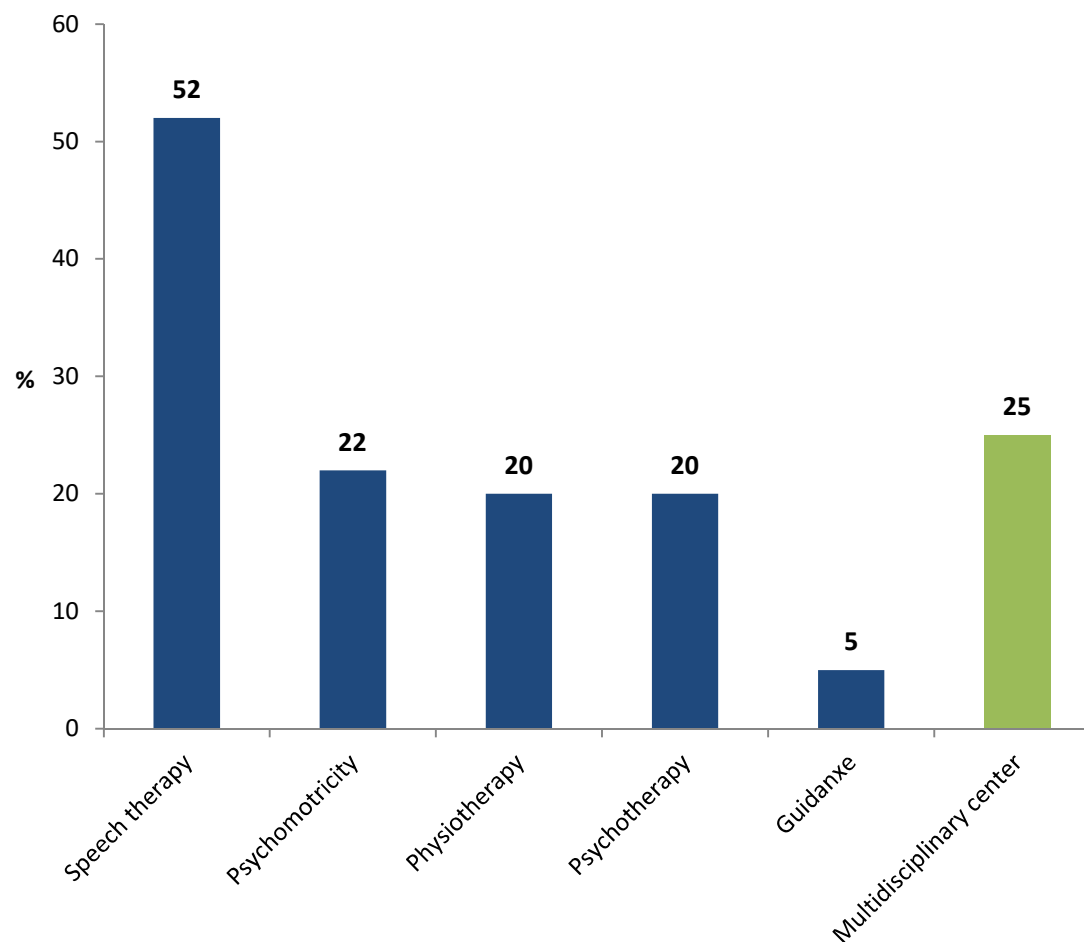


HEALTH SERVICES USE

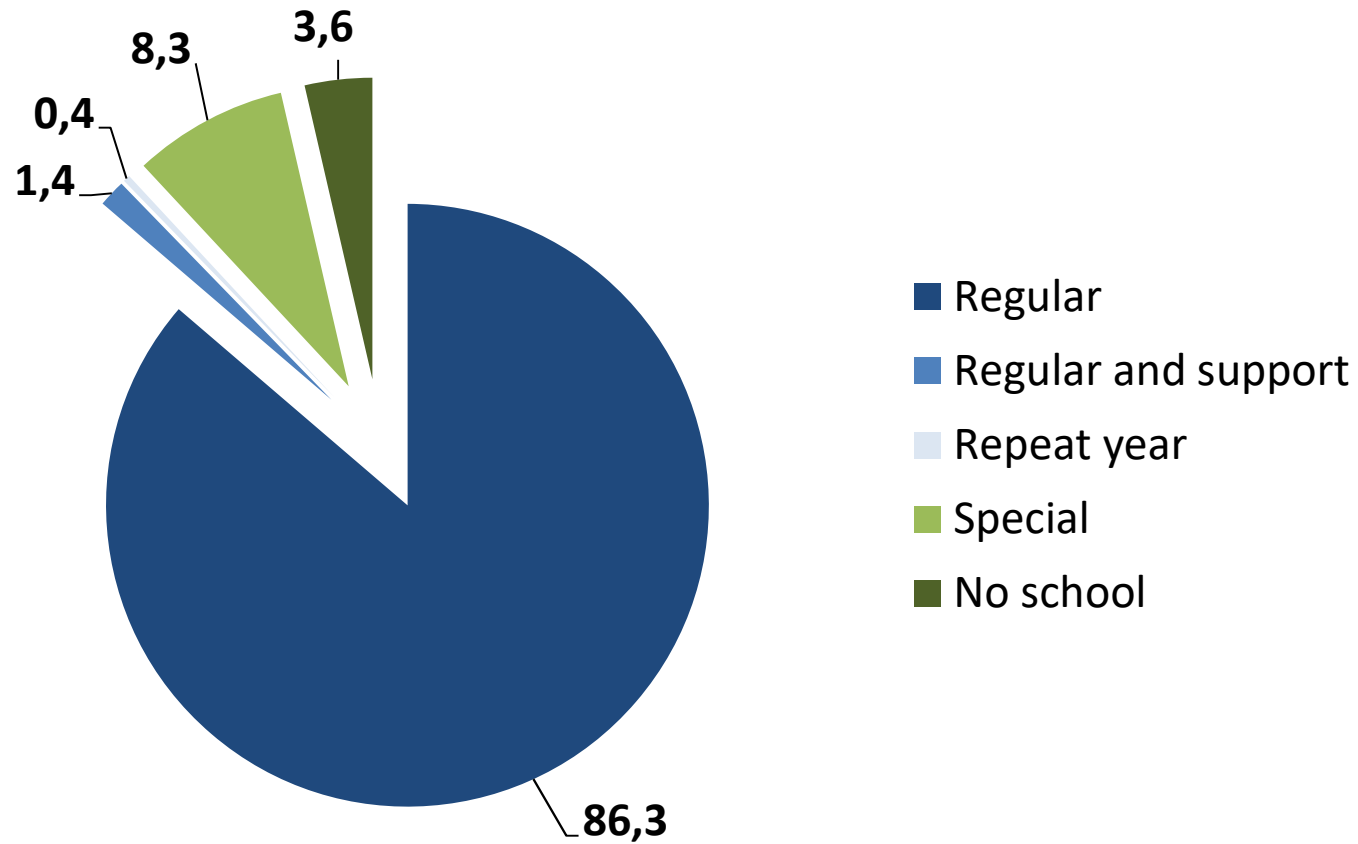
Rehabilitation needed



Type of therapies



SCHOOL ORIENTATION



SUMMARY

	Liege cohort (<32 wk or <1500g) 2012-2014	EPIPAGE (22-32 wk) 1997	Swiss cohort (<30 wk) 2006
Normal or mild disability (%)	84	86	NS
Cerebral palsy (%)	6.6	9	6
Cognitive function (%)			
≥ 85	82	68	75.5
70-84	14.5	21	21
<70	3.1	11	3.5
Moderate- severe visual impairment (%)	2.2	3	0.4
Hearing loss (%)	0.3	<1	0.9
Need for special cares (%)	61	32	27

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Primary school - 8 years

Epipage study group – France

1439 preterm infants born at <32 wk in 1997 out of 2249 eligible survivors (64%)

327 term controls infants out of 555 eligible survivors (59%).

Results :

5% of infants born at <32 weeks GA required specialized school and 18% had repeated a grade versus 1% and 5% for term controls respectively.

Support at school was more frequent in PT infants (15% vs 5%).

Need for special cares **increased** between 5 to 8 years from 32% to 55%.

Larroque et al. – PlosOne 2011

End of primary school - 11 years

Epicure study group – UK

219 of 307 (71%) extremely preterm infants ≤ 25 wk GA compared to 153 classmates.

Results

- Majority of EPT infants were in mainstream school but **2/3 required support**, especially those who **entered education 1 year earlier** due to prematurity.
- Moderate to severe disability in mobility, vision or hearing was rare.
- 40% of infants had moderate to severe **cognitive impairment** (vs 1.3% controls). Difficulties in learning and mathematics were also frequent. Preterm performed better for **sequential tasks** rather than for simultaneous tasks.
- 50% of infants had below average attainment.
- Infants who entered education 1 year earlier due to prematurity re
- Survival but not developmental outcomes improves from 1995 to 2006.

Johnson et al. – Arch Child Dis Fetal Neonat Ed 2009

Secondary school – 12 to 16 years

Meta-analysis of 33 studies on academic performance in preterm infants
Outcomes in reading and mathematics

Results

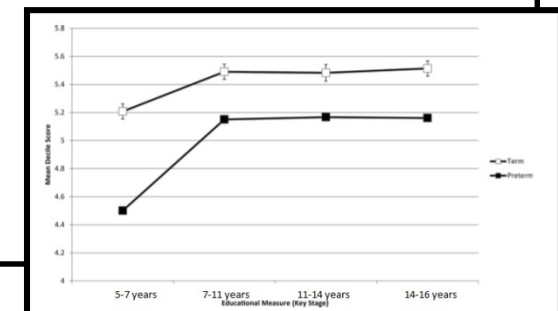
Preterm **reading** deficits were significant but **less pronounced** when children were assessed at 12 to 18 years of age compared to assessment at 5-8 or 9-11 years.

In contrast, the magnitude of deficits in **mathematics** in preterm groups was **similar across age groups**.

McBryde et al. – JAMA network 2020

« **Catch-up** » phenomenon relative to peers mostly occurs during the first years of education compared to secondary stages.

Odd et al – Arch Dis Child 2019



SELF-PERCEIVED HEALTH STATUS AND QUALITY OF LIFE OF ELBW AT ADOLESCENCE

S. Saigal – JAMA 1996

141 of 169 (84%) ELBW born in 1977-1982 compared to 145 controls (Canada)
Age 12-16 years

Health status

27% neurosensory impairment : 13.5% CP – 10% cognitive delay – 10% blindness
94% regular school (integration policy in Ontario)

Functional Level	Cognition		Sensation		Mobility		Self-care		Emotion		Pain	
	ELBW	C†	ELBW	C†	ELBW	C†	ELBW	C†	ELBW	C†	ELBW	C†
Normal or mild impairment, %	89	100	76	90	98	100	95	100	90	94	91	98
Moderate or severe impairment, %	11	0	24	10	2	0	5	0	10	6	9	2
P value	.001		.003		.32		.04		.27		.03	

Some adolescent with NSI did not perceive themselves as limited

SELF-PERCEIVED HEALTH STATUS AND QUALITY OF LIFE OF ELBW AT ADOLESCENCE

S. Saigal – JAMA 1996

Quality of life

ELBW are fairly positive on their HRQL despite NSI :

HRQL $\geq 0,95$ = 71% ELBW vs 73 controls

HRQL $\geq 0,9$ = 72% ELBW vs 76% controls

Higher variability of responses in ELBW cohort

Differences in self-perceived QOL :

- ELBW rated higher score to hypothetical scenarios
- 88% ELBW and 94% controls rated their own HRQL higher than the mean score for the best scenario (Jamie)
- A single ELBW patient scored his QOL as being worse than death.

Jamie

Can see, hear, and talk normally.
Can walk, bend, lift, jump, and run normally.
Happy and not worried most of the time.
Learns and does schoolwork more slowly than the rest of the class.
Can eat, bathe, dress, and use the toilet normally.
Free of pain.

Chris

Can see, hear, and talk normally.
Needs the help of another person, as well as equipment, to walk.
Sometimes angry, worried, or sad.
Can learn and do schoolwork normally without special help.
Can eat, bathe, dress, and use the toilet normally.
Free of pain.

Sandy

Has a problem seeing, hearing, or talking even with glasses or hearing aid.
Needs to use equipment, but not the help of another person, to walk.
Sometimes angry, worried, or sad.
Learns schoolwork very slowly and needs special help.
Needs to use special equipment to eat, bathe, dress, or use the toilet.
Sometimes has pain, maybe needs Tylenol, but the pain doesn't prevent normal activities.

Pat

Blind, deaf, or unable to talk.
Needs to use equipment, but not the help of another person, to walk.
Happy and not worried most of the time.
Learns schoolwork very slowly and needs special help.
Needs help from another person to eat, bathe, dress, or use the toilet.
Sometimes has pain, maybe needs Tylenol, but the pain doesn't prevent normal activities.

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EVOLUTION AT YOUNG ADULTHOOD – THE EPICURE STUDY

At 19 years, former preterm scored significantly lower than term controls across **all neuropsychological tests** with 64% of patients having impairment in at least one domain. Intellectual disability increased from 8.4% to 15.1%.

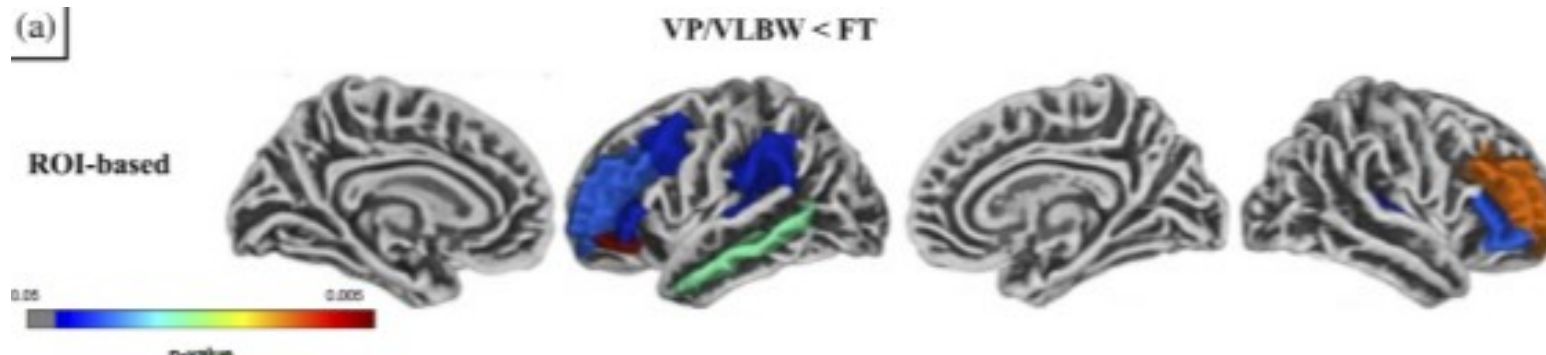
O'Reilly et al. – Pediatrics 2020

Higher behavioral difficulties were noted in preterms compared with controls. Difficulties on home life, friendships, school, works and leisures were mostly triggered by **hyperactivity and peer problems**.

Linsell et al. – European Child & Adolescent Psychiatry 2019

Decreased cortical thickness mediates the relationship between premature birth and cognitive performance in adulthood

Hum Brain Mapp. 2020;41:4952–4963.

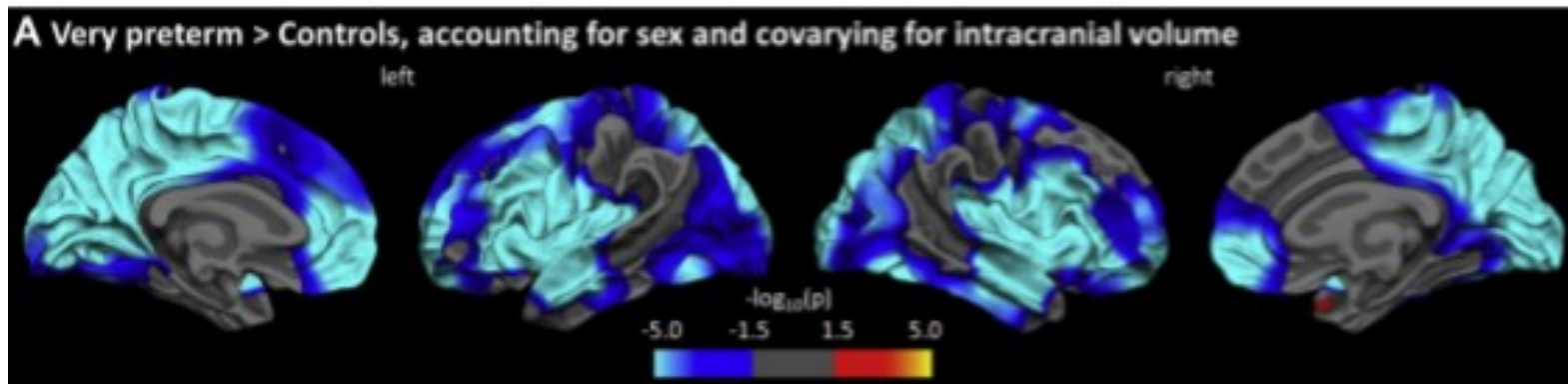


Cortical thickness was reduced in frontal, parietal, and temporal associative cortex predominantly in the left hemisphere in premature-born adults compared to controls.

Full-scale IQ at young adulthood was negatively correlated with cortical thickness in the left hemisphere.

Altered Cortical Gyrification in Adults Who Were Born Very Preterm and Its Associations With Cognition and Mental Health

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging July 2020;



Very preterm infants had significantly lowest local gyrification index in frontal, anterior temporal and occipitoparietal lobes.

Men showed more extensive alterations.

Higher LGI was associated with higher IQ and lower psychopathology scores.

BEHAVIOUR AND SOCIAL OUTCOMES AT ADULTHOOD

A « **global withdrawn personality** » has been described in former VPT/VLBW infants. This profile includes introversion, low risk taking, poor skills in communication and neuroticism.

Eryigit-Madzwamuse, Wolke et al. - Arch Dis Child Fetal Neonatal Ed. 2015

Adults born preterm less often experience **romantic partnership** (OR 0.72), **sexual intercourse** (0.43) and **parenthood** (OR 0.77). However, quality of relationships with partner and friends, when present, was similar to peers born at term.

Mendonça, Wolke et al. – JAMA Network 2019

Preterm birth / low birth weight is associated with lower **educational qualifications**, decreased rate of **employment**, increased risk of receiving **social benefits**. Low childhood IQ was strongly associated with lower adult wealth.

Bilgin, Wolke et al. – Pediatrics 2018

Jaekel, Wolke et al. – Plos One 2019

SELF-PERCEIVED HRQL OF ELBW AT YOUNG ADULTHOOD

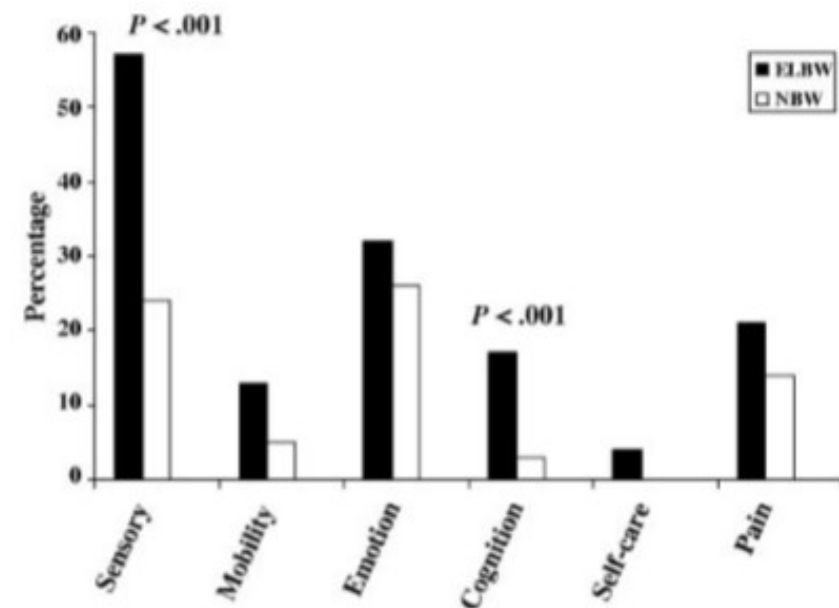
S. Saigal – Pediatrics 2006

143 of 166 (86%) ELBW born in 1977-1982 compared to 130 of 145 controls (89%)
Age 22-26 years

Health status

27% NSI in ELBW vs 2% in controls.

- Higher rates in sensory and cognition limitations in ELBW.
- Perfect health : 24% ELBW vs 46% controls
- Complexity and multiplicity of functional problems in ELBW



SELF-PERCEIVED HRQL OF ELBW AT YOUNG ADULTHOOD

S. Saigal – Pediatrics 2006

Health-related quality of life

TABLE 2 Standard Gamble HRQL Scores for the Self-Reported Health Status of ELBW and NBW YA Respondents

Respondents	n	HRQL Score			p ^a
		Mean ± SD	Median	Mean Difference (95% CI)	
All NBW respondents	130	0.88 ± 0.24	0.95	-0.03 (-0.09 to 0.03)	.32
All ELBW respondents + 10 parent proxies	143	0.85 ± 0.26	0.95		
ELBW respondents without NSIs	105	0.85 ± 0.27		0.006 (-0.09 to 0.10)	.91
ELBW respondents with NSIs (10 proxies)	38	0.85 ± 0.26			

3 ELBW and 2 NBW reported HRQL worse than death (unilateral blindness in 1 ELBW).

Identical decrease of score -0.05 in both cohorts from adolescence to adulthood while adulthood more often requires to face challenges independently.

Personal well-being and life satisfaction is discordant with « objective » health status and disability as viewed by health professionals and society.

Quality of life of adults born very preterm or very low birth weight: A systematic review

Acta Paediatrica. 2020;

Meta-analysis of 18 studies from 11 countries.

Patients ≥ 18 years

Multiple definitions of disabilities and various tests/questionnaire used.

No differences :	11 studies
Lower HRQL in PT :	4 studies
Inconclusive :	3 studies

Conclusion: There is no conclusive evidence that HRQoL differs between term-born adults and those born VPT or with a VLBW. The comparability of studies was restricted by differences between HRQoL measurements, age ranges at assessment and definition of disability.

CHANGING REGARDS ON PREMATURETY, DISABILITY AND OUTCOMES



<http://www.premievoicesbook.com>

KEY MESSAGES

Neurodevelopmental prognosis after very preterm birth is favourable for the **majority** of patients, with high rates of survival without major neurosensory impairment. Risk of disabilities **increases with lower gestational age**.

In Belgium, infants born <32 weeks or <1500g benefit from a **national standardized follow-up until the age of 5 years**. However, some problems such as learning disabilities and behavioural problems can appear in school age. At adolescence and in adulthood, patients born preterm still perform at **lower level** in many areas of development and require **higher level of support** compared to their peers born at term.

Research should focus on **mechanisms** underlying these difficulties and on **educational strategies** to promote catch-up.

Despite neurological impairment, **self-reported health-related quality of life** of former preterm infants is similar to term controls at adulthood.