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## Neurodevelopment and healthcare utilisation at age 5-6 in bronchopulmonary dysplasia: an EPIPAGE-2 cohort study

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**Key words**

Child Development

Epidemiology

Neonatology

**What is already known on this topic**

- Most-of recent work studying neurodevelopmental outcomes in bronchopulmonary dysplasia focus on cognitive and motor skills at age 18-24 months.

**What this study adds**

- At age 5-6, bronchopulmonary dysplasia is strongly and independently associated with behavioural difficulties, lower intelligence quotient score and developmental coordination disorders.
- Even at this age, rehospitalisations for respiratory cause remain frequent and consultation of care providers involved in developmental support is important.

**How this study might affect research, practice or policy**

- Future studies should focus on the development and assessment of early and targeted neurodevelopmental rehabilitation programs for children with BPD.

## **Abstract**

**Objective** We aimed to study neurodevelopmental outcomes and healthcare utilisation at age 5-6 years in very preterm children with BPD.

**Design** Prospective and national population-based study.

**Setting** All the neonatal units in 25 French regions (21 of the 22 metropolitan regions and 4 overseas regions).

**Patients** Children born before 32 weeks' gestation in 2011.

**Interventions** Blind, comprehensive and standardised assessment by trained neuropsychologists and paediatricians at age 5-6.

**Main outcome measures** Overall neurodevelopmental disabilities, behavioural difficulties, developmental coordination disorders, full-scale intelligence quotient, cerebral palsy, social interaction disorders, rehospitalisation in the previous 12 months and detailed developmental support.

**Results:** Of the 3,186 children included, 413 (11.7%) had BPD. The median gestational age of children with BPD was 27 weeks (interquartile range 26.0–28.0) and without BPD was 30 weeks (28.0–31.0). At age 5-6, 3,150 children were alive; 1,914 (60.8%) had a complete assessment. BPD was strongly associated with mild, moderate, and severe overall neurodevelopmental disabilities (odds ratio 1.49, 95% confidence interval 1.05–2.20; 2.20, 1.41–3.42; and 2.71, 1.67–4.40). BPD was associated with developmental coordination disorders, behavioural difficulties, lower intelligence quotient score, as well as rehospitalisation in the last 12 months and developmental support. The association between BPD and cerebral palsy was statistically significant before adjustment but not in adjusted analyses.

**Conclusions:** BPD was strongly and independently associated with many neurodevelopmental disabilities. Improving medical and neurodevelopmental management of BPD in very preterm children should be a priority to reduce its long-term consequences.

## **Introduction**

Preventing the occurrence of neurodevelopmental disabilities is a major issue in very preterm children. In a recent meta-analysis by Twilhaar et al.<sup>1</sup>, BPD was the most important factor contributing to cognitive disabilities. Moreover, despite constant progress in preterm children care, the incidence of BPD remains high. In a systematic review by Siffel et al.<sup>2</sup>, the incidence of BPD ranged from 10% to 89% depending on the definition, gestational age, and country. Knowing the consequences of BPD in terms of neurodevelopmental disabilities and healthcare utilisation is crucial to organise both the follow-up and rehabilitation of preterm children.

Among other factors, the survival of children with lower gestational age<sup>3</sup>, increased non-invasive supports<sup>4</sup> and new ventilation devices may have changed the consequences of BPD. Furthermore, in many recent studies<sup>5,6</sup>, whose recruitment took place in the 2010s, neurodevelopmental follow-up of children with BPD ended at age 18 to 24 months, when developmental assessment is still incomplete, and most-of studies focused on motor<sup>7</sup> and cognitive disabilities<sup>1</sup>. No recent study has analysed the association of BPD with behavioural difficulties or social interaction disorders after age 2.

This study aimed to investigate neurodevelopmental outcomes and healthcare utilisation at age 5-6 in children with BPD from a large 2010s cohort of very preterm children

## **Methods**

### Study Design and Participants

The study population was from the French national population-based and prospective cohort EPIPAGE-2 (*Etude épidémiologique sur les Petits Ages GEstationnels-2*), whose recruitment took place in 2011. The EPIPAGE-2 cohort study protocols<sup>8</sup>, neonatal survival and morbidity<sup>3</sup>, and global outcomes at age 5-6<sup>9</sup> for the overall cohort are described

elsewhere. Children were eligible for this study if they were born before 32 weeks' gestation and were alive at 36 weeks' postmenstrual age (PMA). We excluded those with congenital pulmonary and brain malformations (n=35) and those with missing respiratory support status at 36 weeks' PMA (n=78) (Figure 1).

### Exposure

BPD was defined as any respiratory support, including invasive or non-invasive ventilation or supplemental oxygen, at 36 weeks' PMA<sup>10</sup>. The 2001 National Institute of Child Health and Human Development (NICHD) definition of BPD<sup>11</sup> was used in sensitivity analyses.

### Outcomes

#### *Neurodevelopmental outcomes*

Between age 5 and 6, children were blindly assessed by trained neuropsychologists and paediatricians, and parents answered a questionnaire concerning the child's lifestyle, health, and medical follow-up. If the centre-based assessment was not possible, a questionnaire was mailed to the families. The different areas of neurodevelopment were screened. Visual disabilities were assessed with the Sander-Zanlonghi scale<sup>12</sup>, and hearing disabilities were defined by hearing loss > 40 dB not corrected or partially corrected with a hearing aid. Developmental coordination disorders were assessed with the Movement Assessment Battery for Children, second edition<sup>13</sup>, and cerebral palsy with the Gross Motor Function Classification System<sup>14</sup>. Behavioural difficulties were scored with the Strengths and Difficulties Questionnaire<sup>15</sup>. Full-scale intelligence quotient was calculated with the Wechsler Intelligence Scale for Children, fourth edition<sup>16</sup>. Social interaction disorders were assessed with the Social Communication Questionnaire<sup>17</sup> and by parents' reported diagnosis of autism spectrum disorders.

A composite outcome for overall neurodevelopmental disabilities was built. Moderate and severe overall neurodevelopmental disabilities were defined based on the severity of cognitive disorders,

cerebral palsy and sensory impairments. Behavioural difficulties and developmental coordination disorders were added to the definition of mild overall neurodevelopmental disabilities with mild cerebral palsy, cognitive disorders and sensory impairment. The detailed classification of overall neurodevelopmental disabilities in the EPIPAGE-2 cohort has been published by Pierrat et al.<sup>9</sup> To define the thresholds of the different neurodevelopmental scales, term-born children from the French ELFE (*Étude Longitudinale Française depuis l'Enfance*) cohort<sup>18</sup> were assessed with the EPIPAGE-2 cohort study protocols. The recruitment of the two cohorts was contemporary.

#### *Healthcare utilisation*

Healthcare utilisation data in the previous 12 months were collected in the parental questionnaire and included hospitalisations, consultations with neuropaediatricians and pneumopaediatricians, and consultations with care providers specialised in developmental interventions. School enrolment and any schooling support were also reported.

A composite outcome for developmental support<sup>9</sup> consisting of at least two consultations in the previous 12 months with a care provider specialised in developmental interventions or care in a rehabilitation centre or any schooling support was built.

#### Statistical analyses

The perinatal and sociodemographic characteristics of the population are described. All percentages were weighted over the recruitment time<sup>8</sup> (weighting factor 1.35 for children born between 28- and 31-weeks' gestation). Mortality between 36 weeks' PMA and age 5-6 is reported. Neurodevelopmental disabilities and healthcare utilisation of surviving children at age 5-6 are described according to BPD status and bivariable analyses are reported. P-value were calculated with Pearson's chi-squared and Wilcoxon tests for categorical and continuous variables. To assess the association between BPD and neurodevelopmental outcomes as well as healthcare utilisation at age 5-6, multivariable models were built with



Generalised Estimating Equations to account for multiple births. Based on a review of literature a directed acyclic graph (Figure S1) was constructed<sup>19,20</sup> to choose the adjustment variables, which were gestational age, sex, small-for-gestational-age, antenatal corticosteroids use, hemodynamic disorders, patent ductus arteriosus, necrotizing enterocolitis, late-onset sepsis, intraventricular hemorrhage, extra-uterine growth restriction, and maternal country of birth and educational level. Missing data at age 5-6 were accounted for with multiple imputations by chain equations. The variables included in the imputation models were those predicting loss to follow-up and age 5-6 outcomes (Table S1). A total of 60 datasets were imputed, with 40 iterations for each. Analyses were performed on each imputed dataset and results were combined using Rubin's rules<sup>21</sup>. To assess the impact of multiple imputations, perinatal characteristics of children with complete data at age 5-6 were compared to those of children with missing outcomes and complete-case analyses were reported. Exploratory subgroup analyses in children born before 29 weeks' gestation were performed. Sensitivity analyses were carried out using the 2001 NICHD definition of BPD<sup>11</sup>. For all analyses, significance was set at  $p < .05$  and R 4.1.2 (R Core team) was used.

### Ethical agreement

The collection and analysis of data for children at age 5-6 was approved by the National Data Protection Authority (CNIL DR-2016-290) and by French ethics committees.

### **Results**

The study population consisted of 3,186 very preterm children alive at 36 weeks' PMA (Figure 1): 413 (11.7%) had BPD. The median gestational age of children with BPD was 27 weeks, (interquartile range 26.0–28.0) compared to 30 weeks (28.0–31.0) for children without BPD. Perinatal and sociodemographic characteristics of the population are listed in

Table 1. Among children with and without BPD, mortality rate between 36 weeks' PMA and age 5-6 was 4.3% (19/413) and 0.6% (17/2,773) ( $p < 0.001$ ).

A complete neurodevelopmental assessment was available for 60.8% (1,914/3,150) of the children alive at age 5-6. Among the 39.2% (1,236/3,150) of children with missing outcomes, some information was available from mailed questionnaires for 20.6% (254/1,236) and from partial centre-based assessment for 6.5% (80/1,236) (Figure 1). Compared to complete-case children, those included in the analyses by multiple imputation had less often intraventricular hemorrhage and a lower socio-economic status (Table S2).

#### Neurodevelopmental outcomes for survivors at age 5-6 years

Among children with BPD, only 28.0% (95% confidence interval [CI] 22.9–33.1) did not have overall neurodevelopmental disabilities as compared with 46.8% (95% CI 44.6–49.1) of children without BPD. Children with BPD had more often developmental coordination disorders, behavioural difficulties, impaired intellectual quotient, cerebral palsy and social interaction disorders (imputed results). All imputed and complete-case neurodevelopmental outcomes at age 5-6 are detailed by BPD status in (Table 2). In imputed multivariable models (Table 3), BPD was strongly associated with mild (OR 1.49, 95% CI 1.05–2.20), moderate (OR 2.20, 95% CI 1.41–3.42), and severe overall neurodevelopmental disabilities (OR 2.71, 95% CI 1.67–4.40). When detailing the type of neurodevelopmental disorder involved, BPD was strongly and independently associated with behavioural difficulties, lower intelligence quotient score and developmental coordination disorders. Association with cerebral palsy was no more-significant in imputed data after adjustment on potential confounders. Complete-case analyses results were consistent with those obtained after multiple imputations (Table 3).

#### Healthcare utilisation for survivors at age 5-6 years

Hospitalisation during the 12 months before the age 5-6 evaluation occurred in 21.8% (95% CI 16.9–26.7) of children with BPD and 13.3% (95% CI 11.7–15.0) without BPD. Among children with BPD, only 22.3% (95% CI 16.8–27.8) were followed up by a paediatric pneumologist. Developmental support was provided to 61.9% (95% CI 56.3–67.5) of children with BPD and 42.3% (95% CI 40.0–44.6) without BPD (imputed results). All imputed and complete-case healthcare utilisation outcomes are described in (Table 2). In imputed multivariable models, BPD was associated with hospitalisations in the previous 12 months and developmental support. For developmental support, at age 5-6, BPD was associated with consultation in the last 12 months with a psychomotor therapist or motor physiotherapist, speech therapist and respiratory therapist. BPD was not associated with follow-up in a rehabilitation centre. Complete-case analyses results were consistent with those obtained after multiple imputations (Table 3).

#### Subgroup analyses

Among children born before 29 weeks' gestation, 343/1,245 (25.9%) had BPD. In imputed multivariable models, BPD was associated with moderate (OR 2.57, 95% CI 1.53-4.34) and severe (OR 2.96, 95% CI 1.66-3.50) overall neurodevelopmental disabilities. For healthcare utilisation, BPD was associated with developmental support (OR 1.90, 95% CI 1.35-2.67) (Table S3).

#### Sensitivity analyses: NICHD BPD definition

Respectively 499/3,103 (15.1%), 122/3,103 (3.6%) and 262/3,103 (7.6%) of children had mild, moderate and severe BPD according to the 2001 NICHD definition<sup>11</sup>. Association between BPD defined with the 2001 NICHD consensus and age 5-6 outcomes is reported in Table S4. In imputed multivariable models, severe BPD was associated with mild (OR 1.72, 95% CI 1.10-2.69), moderate (OR 2.91, 95% CI 1.70-4.97) and severe (OR 2.98, 95% CI 1.57-

5.65) overall neurodevelopmental disabilities. For healthcare utilisation, severe BPD was associated with developmental support (OR 1.86, 95% CI 1.29-2.68).

## **Discussion**

In a large and population-based prospective cohort study, we found at age 5-6 a strong and independent association of BPD defined as any respiratory support at 36 weeks' PMA with many neurodevelopmental outcomes including behavioural difficulties, full-scale intelligence quotient and developmental coordination disorders as well as healthcare utilisation.

The main finding was the strength of the association between BPD and neurodevelopmental disabilities and the range of neurodevelopmental domains involved. After adjusting for the known confounders, the intelligence quotient was 4.8 points lower for children with than without BPD, which is less than that in a meta-analysis by Twilhaar et al.<sup>1</sup>, finding a 15-point intelligence quotient difference, but these meta-analysis results were not adjusted for sociodemographic or medical history. For motor skills, BPD was associated with developmental coordination disorders, which is rarely reported in the literature. We also found an independent association with behavioural difficulties, which agrees with other work<sup>22</sup>. The important question we cannot answer is that of causality, even if we can give some hints. The temporality of the BPD-neurodevelopmental disabilities association, its strength, and its stability in different populations<sup>1,7</sup> are compatible with a causal link. Similarly, the dose-response relationship found in our work and in other works<sup>23</sup> using the 2001 NIHCD definition of BPD, the existence of different hypotheses to explain the association, such as white-matter injury secondary to hypoxia or inflammation<sup>24</sup>, postnatal corticosteroid therapies<sup>25</sup> or delayed neonatal unit discharge and rehospitalisations, are consistent with this hypothesis.

The second finding was the importance of healthcare utilisation related to BPD. Increased healthcare costs is well described in children with BPD<sup>26</sup>, but to our knowledge, consultation with the different care providers at the pre-school age is less reported. After controlling for confounding factors, at age 5-6, children with BPD were more likely to receive psychomotor therapy or motor physiotherapy and speech therapy than those without BPD. The various care providers consulted confirm the extent of neurodevelopmental disabilities associated with BPD. Of note, BPD was not associated with more follow-up in rehabilitation centres, which are multidisciplinary centres allowing for coordinated action by health actors dealing with the development of children. However, Sheperd et al.<sup>27</sup> showed that a comprehensive chronic care program strongly decreased the Bayley score to < 70 at age 18 to 24 months in children with BPD. Increasing the follow-up in rehabilitation centres for children with BPD may be a way to improve their neurodevelopmental outcomes. Our study revealed that even at age 5-6, BPD was independently associated with more frequent rehospitalisation in the last 12 months. This result shows in children with BPD the persistence of fragility even several years after discharge from neonatal care units. Improving the management of respiratory symptoms, compliance, and long-term prevention of respiratory tract infections in these children may be a way to decrease rehospitalisations.

### Strengths and limits

This study has several strengths. The EPIPAGE-2 cohort is a national prospective population-based cohort with detailed data collection in the antenatal and postnatal period. Therefore, we could consider all known confounders. In addition, the use of a directed acyclic graph for selecting the adjustment variables decreases the risk of residual confounding bias and overfitting. For example, we didn't adjust analyses on postnatal corticosteroids because it is probably a mediator of the BPD–neurodevelopmental outcomes association rather than a

confounder. The definition used for BPD was the one that predicted best respiratory morbidity at 18 to 26 months' corrected age in a recent publication<sup>10</sup> and the 5-6 years assessment was blinded and standardised, involved validated tools, and was performed by trained professionals. In addition, we comprehensively analysed the neurodevelopmental morbidity due to BPD. Many studies only assessed the cognitive or motor outcomes of children, but we were also able to analyse the associations between BPD status and behaviour, social interaction disorders and healthcare utilisation.

Nevertheless, the study has some limitations. Missing data rate for the main outcomes at age 5-6 was high (39%). However, this rate corresponds to the usual lost to follow-up rate in cohorts of preterm children<sup>28</sup>. Furthermore, we accounted for the risk of attrition bias by using multiple imputations for missing outcomes, which is particularly important when examining developmental outcomes in cohorts of very preterm children because of systematic differences in sociodemographic characteristics of children lost to follow-up<sup>28</sup>. Another limitation was the lack of detail in our data on respiratory support at 36 weeks' PMA. To assess the impact of BPD severity on outcomes at age 5-6, we could not use the Jensen definition<sup>10</sup>. This definition was after the creation of the EPIPAGE-2 cohort and we did not have the flow of the nasal cannula at 36 days' gestation to differentiate between Jensen grade 1 and 2 BPD. Nevertheless, we used the NIHCD severity definition<sup>11</sup>, which is still widely used in the literature.

### Implications for future

In association with the works on BPD's prevention, future studies should focus on the development and assessment of early and targeted neurodevelopmental rehabilitation programs for children with respiratory support at 36 weeks' PMA. A comprehensive follow-

up, both pulmonary and neurodevelopmental, of children with this chronic lung disease appears to be crucial.

### **Conclusion**

BPD was strongly and independently associated with many neurodevelopmental outcomes.

Improving both the prevention of BPD and the medical and neurodevelopment management of children with BPD should be a priority to reduce the long-term consequences of this disease.

**Table 1. Description of very preterm children according to bronchopulmonary dysplasia (BPD) status. (n=3,186)**

|   | No BPD<br>N = 2,773 (87.0%) | BPD<br>N = 413 (13.0%) | P-value <sup>a</sup> |
|---|-----------------------------|------------------------|----------------------|
| <b>Perinatal characteristics</b>                            |                             |                        |                      |
| Male, n/N (% <sup>b</sup> )                                 | 1,441/2,773 (52.0)          | 223/413 (54.6)         | 0.35                 |
| Gestational age (weeks), n/N (% <sup>b</sup> )              |                             |                        |                      |
| 24-25 <sup>c</sup>  | 3.3 (121/2,773 (3.3))       | 106/413 (22.1)         | <0.001               |
| 26-27   | 441/2,773 (14.5)            | 182/413 (42.9)         |                      |
| 28-29   | 780/2,773 (29.0)            | 83/413 (23.3)          |                      |
| 30-31   | 1,431/2,773 (53.1)          | 42/413 (11.8)          |                      |
| Small-for-gestational age, n/N (% <sup>b</sup> )            | 911/2,773 (33.4)            | 179/413 (45.8)         | <0.001               |
| ≥ 1 antenatal corticosteroids course, n/N (% <sup>b</sup> ) | 1,821/2,687 (67.9)          | 279/400 (70.1)         | 0.40                 |
| Surfactant administration, n/N (% <sup>b</sup> )            | 1,609/2,748 (57.5)          | 393/409 (95.7)         | 0.94                 |
| Hemodynamic disorders, n/N (% <sup>b</sup> )                | 566/2,698 (20.2)            | 227/407 (54.4)         | <0.001               |
| Intraventricular hemorrhage grade, n/N (% <sup>b</sup> )    |                             |                        |                      |
| No IVH  | 1,867/2,732 (68.9)          | 224/413 (54.1)         | <0.001               |
| Grade 1   | 465/2,732 (17.0)            | 88/413 (21.8)          |                      |
| Grade 2   | 313/2,732 (11.0)            | 71/413 (16.9)          |                      |
| Grade 3   | 62/2,732 (2.2)              | 22/413 (5.2)           |                      |
| Grade 4   | 25/2,732 (0.8)              | 8/413 (1.9)            |                      |
| Patent ductus arteriosus treatment, n/N (% <sup>b</sup> )   | 518/2,2697 (18.0)           | 267/405 (64.0)         | <0.001               |
| Necrotizing enterocolitis, n/N (% <sup>b</sup> )            | 97/2,745 (3.5)              | 24/411 (5.9)           | 0.02                 |
| Late-onset sepsis, n/N (% <sup>b</sup> )                    | 497/2,743 (17.3)            | 195/407 (46.6)         | <0.001               |
| Extra-uterine growth restriction, n/N (% <sup>b</sup> )     |                             |                        |                      |
| No  | 1,148/2,422 (47.0)          | 263/402 (65.0)         | <0.001               |
| Moderate  | 624/2,422 (25.6)            | 81/402 (20.2)          |                      |
| Severe  | 650/2,422 (27.4)            | 58/402 (14.8)          |                      |
| Postnatal corticosteroids, n/N (% <sup>b</sup> )            | 97/2,696 (3.3)              | 134/407 (31.8)         | <0.001               |
| <b>Maternal sociodemographic characteristics</b>            |                             |                        |                      |
| Educational level, n/N (% <sup>b</sup> )                    |                             |                        |                      |
| < Secondary school  | 853/2,560 (33.4)            | 131/370 (35.2)         | 0.49                 |
| Secondary school  | 565/2,560 (22.1)            | 69/370 (18.5)          |                      |
| 1 or 2 years post-secondary school                          | 484/2,560 (18.8)            | 69/370 (18.9)          |                      |
| ≥ 3 years post-secondary school                             | 658/2,560 (25.7)            | 101/370 (27.4)         |                      |
| Country of birth, n/N (% <sup>b</sup> )                     |                             |                        |                      |
| France  | 2,080/2,7423 (76.0)         | 319/407 (78.6)         | 0.42                 |
| Other European country                                      | 68/2,743 (2.5)              | 12/407 (2.9)           |                      |
| North Africa country  | 232/2,743 (8.5)             | 27/407 (6.7)           |                      |
| Other African country                                       | 211/2,743 (7.5)             | 34/407 (8.1)           |                      |
| Other   | 152/2,743 (5.5)             | 15/407 (3.7)           |                      |

Bronchopulmonary dysplasia was defined using Jensen et al. 2019 definition at 36 weeks' postmenstrual age. Extra-uterine growth restriction between birth and 36 weeks' postmenstrual age was defined with the Patel et al. method (Patel et al. Pediatrics 2005). Intraventricular grades were defined with the Papile classification (Papile, 1978). Necrotizing enterocolitis corresponded to all necrotizing enterocolitis grade ≥ 2 from the Bell classification (Bell, 1978). Patent ductus arteriosus was defined a requiring medical or surgical treatment. Small-for-gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves (Ego, 2016).

<sup>a</sup> Pearson's chi-squared test for categorical variables.

<sup>b</sup> All percentages and means were weighted over the recruitment time (weighting factor 1.35 for children born at 27-31-weeks' gestation).

<sup>c</sup> Including 5 children born before 24 weeks' gestation, with one survivor at age 5-6 years born at 23 weeks' and 6 days' gestational age.



**Table 2. Neurodevelopmental outcomes and healthcare consumption by bronchopulmonary dysplasia (BPD) status for very preterm children alive at age 5-6 years. (n=3,150)**

|  | Complete-case<br>n/N (%) <sup>a, b</sup> |                       |                      | Imputed data<br>% (95% CI) <sup>a</sup> |                       |                      |
|--|--|-----------------------|----------------------|---|-----------------------|----------------------|
|  | No BPD<br>N= 2,756 (87.5%)               | BPD<br>N= 394 (12.5%) | P-value <sup>c</sup> | No BPD<br>N= 2,756 (87.5%)              | BPD<br>N= 394 (12.5%) | P-value <sup>c</sup> |
| <b>Neurodevelopmental outcomes</b>                                 |  |                       |                      |   |                       |                      |
| Overall neurodevelopmental disabilities <sup>d</sup>               |  |                       |                      |   |                       |                      |
| None   | 839/1,666 (50.5)                         | 83/248 (33.9)         | <0.001               | 46.8 (44.6-49.1)                        | 28.0 (22.9-33.1)      | <0.001               |
| Mild   | 599/1,666 (35.8)                         | 98/248 (39.5)         |                      | 35.2 (33.0-37.4)                        | 37.4 (31.6-43.1)      |                      |
| Moderate   | 149/1,666 (9.0)                          | 38/248 (15.0)         |                      | 10.5 (9.0-11.9)                         | 17.2 (12.9-21.5)      |                      |
| Severe   | 79/1,666 (4.7)                           | 29/248 (11.6)         |                      | 7.4 (6.1-8.8)                           | 17.4 (12.8-22.0)      |                      |
| Developmental coordination disorders <sup>e</sup> (N= 1,538)       |  |                       |                      |   |                       |                      |
| Total MABC-2 score $\leq$ 5 <sup>th</sup> centile <sup>f</sup>     | 106/1,349 (7.6)                          | 31/170 (17.6)         | <0.001               | 16.2 (14.2-18.2)                        | 36.4 (30.3-42.5)      | <0.001               |
| Behavioural difficulties   |  |                       |                      |   |                       |                      |
| Total SDQ score $\geq$ 90 <sup>th</sup> centile <sup>f</sup>       | 162/1,683 (9.7)                          | 39/252 (15.6)         | 0.005                | 11.4 (9.8-13.0)                         | 17.7 (13.2-22.3)      | 0.003                |
| Full-scale intelligence quotient <sup>g</sup>                      |  |                       |                      |   |                       |                      |
| Mean (SD)  | 96.4 (14.9)                              | 91.0 (16.7)           | <0.001               | 94.3 (16.0)                             | 86.7 (18.3)           | <0.001               |
| Total intelligence quotient score $<$ -2 SD <sup>f</sup> ( $<$ 79) | 181/1,678 (10.8)                         | 54/244 (21.6)         | <0.001               | 14.8 (13.0-16.5)                        | 30.0 (24.5-35.5)      | <0.001               |
| Moderate or severe visual disability <sup>h</sup>                  | 9/1,702 (0.5)                            | 2/242 (0.8)           | 0.55                 | 1.4 (0.7-2.1)                           | 2.5 (0.3-4.7)         | 0.24                 |
| Moderate or severe hearing disability <sup>i</sup>                 | 9/1,888 (0.5)                            | 11/283 (3.9)          | <0.001               | 0.7 (0.3-1.1)                           | 4.3 (2.0-6.6)         | <0.001               |
| Cerebral palsy   |  |                       |                      |   |                       |                      |
| All cerebral palsy   | 98/1,939 (5.0)                           | 32/290 (11.0)         | <0.001               | 7.8 (6.5-9.1)                           | 16.3 (11.9-20.6)      | <0.001               |
| By categories  |  |                       |                      |   |                       |                      |
| No cerebral palsy  | 1,841/1,939 (95.0)                       | 258/290 (89.0)        | <0.001               | 92.2 (90.9-93.5)                        | 83.7 (79.4-88.1)      | <0.001               |
| Cerebral palsy GMFCS-1   | 43/1,939 (2.1)                           | 11/290 (3.7)          |                      | 2.5 (1.8-3.2)                           | 5.6 (2.9-8.4)         |                      |
| Cerebral palsy GMFCS-2/5   | 55/1,939 (2.9)                           | 21/290 (7.3)          |                      | 5.3 (4.2-6.4)                           | 10.6 (6.9-14.3)       |                      |
| Epilepsy   | 20/1,688 (1.1)                           | 3/252 (1.1)           | 0.99                 | 2.4 (1.3-3.4)                           | 3.9 (1.0-6.9)         | 0.24                 |
| Social interaction disorders                                       |  |                       |                      |   |                       |                      |
| Autism spectrum disorders reported by parents                      | 17/1,719 (1.0)                           | 7/259 (2.8)           | 0.02                 | 1.9 (1.0-2.8)                           | 4.3 (1.5-7.1)         | 0.04                 |
| SCQ score $\geq$ 90 <sup>th</sup> centile <sup>f</sup>             | 291/1,618 (18.0)                         | 50/244 (20.3)         | 0.39                 | 21.4 (19.3-23.5)                        | 26.9 (21.0-32.9)      | 0.06                 |

**Table 2. Neurodevelopmental outcomes and healthcare consumption by bronchopulmonary dysplasia (BPD) status for very preterm children alive at age 5-6 years. (n=3,150) (continued)**

|   | Complete-case<br>n/N (%) <sup>a, b</sup> |                       |                      | Imputed data<br>% (95% CI) <sup>a</sup> |                       |                      |
|---|--|-----------------------|----------------------|---|-----------------------|----------------------|
|   | No BPD<br>N= 2,756 (87.5%)               | BPD<br>N= 394 (12.5%) | P-value <sup>c</sup> | No BPD<br>N= 2,756 (87.5%)              | BPD<br>N= 394 (12.5%) | P-value <sup>c</sup> |
| <b>Healthcare utilisation</b>                                     |  |                       |                      |   |                       |                      |
| Hospitalisation in the last 12 months                             | 225/1,867 (12.0)                         | 53/279 (19.2)         | 0.001                | 13.3 (11.7-15.0)                        | 21.8 (16.9-26.7)      | <0.001               |
| For respiratory diagnoses   | 28/225 (12.8)                            | 10/53 (17.1)          | 0.37                 | 16.0 (11.4-20.7)                        | 22.0 (10.5-33.5)      | 0.07                 |
| Consultation with a paediatric neurologist in the last 12 months  | 121/1,837 (6.5)                          | 34/269 (12.5)         | <0.001               | 8.7 (7.3-10.1)                          | 16.9 (11.8-22.0)      | <0.001               |
| Consultation with a paediatric pneumologist in the last 12 months | 111/1,502 (7.3)                          | 46/223 (20.3)         | <0.001               | 8.1 (6.6-9.6)                           | 22.3 (16.8-27.8)      | <0.001               |
| Developmental support <sup>j</sup>                                | 723/1,795 (39.9)                         | 163/274 (58.6)        | <0.001               | 42.3 (40.0-44.6)                        | 61.9 (56.3-67.5)      | <0.001               |
| Details of the developmental supports                             |  |                       |                      |   |                       |                      |
| Psychologist or psychiatrist <sup>k</sup>                         | 327/1,823 (17.8)                         | 71/265 (26.6)         | <0.001               | 20.7 (18.7-22.7)                        | 30.9 (25.3-36.5)      | <0.001               |
| Psychomotor therapist or motor physiotherapist <sup>k</sup>       | 331/1,811 (17.9)                         | 99/269 (35.7)         | <0.001               | 21.9 (20.0-23.8)                        | 41.5 (35.8-47.1)      | <0.001               |
| Speech therapist <sup>k</sup>                                     | 420/1,825 (22.7)                         | 116/268 (43.0)        | <0.001               | 25.2 (23.3-27.2)                        | 46.7 (40.8-52.7)      | <0.001               |
| Respiratory physiotherapist <sup>k</sup>                          | 56/1,837 (3.1)                           | 13/271 (4.8)          | 0.14                 | 8.9 (7.4-10.4)                          | 19.2 (14.3-24.1)      | <0.001               |
| Follow-up in rehabilitation centre <sup>k, l</sup>                | 290/1,766 (16.2)                         | 62/262 (23.6)         | 0.003                | 24.9 (22.8-27.1)                        | 35.8 (30.0-41.6)      | <0.001               |
| Any schooling support   | 199/1,887 (10.3)                         | 59/282 (20.6)         | <0.001               | 14.0 (11.9-16.1)                        | 26.4 (20.7-32.1)      | <0.001               |

GMFCS=Gross Motor Function Classification System; MABC-2=Movement assessment battery for children, 2nd edition; SCQ=Social Communication Questionnaire; SDQ=Strengths and Difficulties Questionnaire

<sup>a</sup> All percentages and means were weighted over the recruitment time (weighting factor 1.35 for children born at 27-31-weeks' gestation).

<sup>b</sup> In the complete-case results, denominator can differ between variables because of missing data.

<sup>c</sup> Pearson's chi-squared test for categorical variables and Wilcoxon test for continuous variable.

<sup>d</sup> Includes cerebral palsy, vision, hearing, full-scale intelligence quotient, developmental coordination disorders, and behavioural difficulties.

<sup>e</sup> Among children without cerebral palsy, severe or moderate sensory disabilities, and full-scale intelligence quotient > -2 SD of the distribution related to the reference group born at term.

<sup>f</sup> Cut-off point of the distribution related to the reference group born at term (37-41 weeks)

<sup>g</sup> Full-scale intelligence quotient, measured by the Wechsler Preschool and Primary Scale of Intelligence, 4th edition.

<sup>h</sup> Moderate or severe visual disability was defined as binocular visual acuity <3.2/10.

<sup>i</sup> Moderate or severe hearing disability was defined as uni- or bilateral hearing loss (> 70 dB) not corrected or partially corrected with hearing aid.

<sup>j</sup> Developmental support was defined as at least two consultations with a psychologist, psychiatrist, orthoptist, speech therapist, psychomotor therapist, physiotherapist, during the last 12 months or schooling in a special school or follow-up in any type of rehabilitation centre.

<sup>k</sup> At least one consultation in the last 12 months.

<sup>l</sup> Any type of rehabilitation centre.

**Table 3. Association between bronchopulmonary dysplasia (BPD) and outcomes for very preterm children alive at age 5-6 years.**

|  | Complete-case<br>N= 1,914                  |                      | Imputed data<br>N= 3,150                   |                      |
|--|--|----------------------|--|----------------------|
|  | BPD<br>N= 248<br>aOR <sup>a</sup> (95% CI) | P-value <sup>b</sup> | BPD<br>N= 394<br>aOR <sup>a</sup> (95% CI) | P-value <sup>b</sup> |
| <b>Neurodevelopmental outcomes</b>                                 |  |                      |  |                      |
| Overall neurodevelopmental disabilities <sup>c</sup>               |  |                      |  |                      |
| None   | 1  | 0.01                 | 1  | <0.001               |
| Mild   | 1.34 (0.91-1.95)                           |                      | 1.49 (1.05-2.20)                           |                      |
| Moderate   | 2.10 (1.24-3.57)                           |                      | 2.20 (1.41-3.42)                           |                      |
| Severe   | 2.46 (1.28-4.72)                           |                      | 2.71 (1.67-4.40)                           |                      |
| Developmental coordination disorders <sup>d</sup>                  |  |                      |  |                      |
| Total MABC-2 score $\leq$ 5 <sup>th</sup> centile <sup>e</sup>     | 1.62 (0.94-2.80)                           | 0.08                 | 1.79 (1.14-2.83)                           | 0.01                 |
| Behavioural difficulties:  |  |                      |  |                      |
| Total SDQ score $\geq$ 90 <sup>th</sup> centile <sup>e</sup>       | 1.86 (1.11-3.12)                           | 0.02                 | 1.67 (1.11-2.50)                           | 0.01                 |
| Full-scale intelligence quotient <sup>f</sup>                      |  |                      |  |                      |
| Total intelligence quotient score ( $\beta$ )                      | -3.4 (-5.9 to -0.9)                        | 0.008                | -4.8 (-7.2 to -2.4)                        | <0.001               |
| Total intelligence quotient score $<$ -2 SD ( $<$ 79) <sup>e</sup> | 1.86 (1.16-2.99)                           | 0.01                 | 1.97 (1.38-2.81)                           | <0.001               |
| Cerebral palsy   |  |                      |  |                      |
| All cerebral palsy   | 1.24 (0.71-2.18)                           | 0.45                 | 1.52 (0.98-2.35)                           | 0.06                 |
| By categories  |  |                      |  |                      |
| No cerebral palsy  | 1  | 0.02                 | 1  | 0.15                 |
| Cerebral palsy GMFCS-1   | 0.49 (0.16-1.43)                           |                      | 1.27 (0.59-2.72)                           |                      |
| Cerebral palsy GMFCS-2/5   | 2.19 (1.19-4.03)                           |                      | 1.64 (0.98-2.74)                           |                      |
| Social interaction disorders                                       |  |                      |  |                      |
| SCQ score $\geq$ 90 <sup>th</sup> centile <sup>e</sup>             | 1.18 (0.77-1.80)                           | 0.45                 | 1.23 (0.86-1.76)                           | 0.26                 |
| <b>Healthcare utilisation</b>                                      |  |                      |  |                      |
| Hospitalisation in the last 12 months                              | 1.58 (1.04-2.40)                           | 0.03                 | 1.48 (1.03-2.11)                           | 0.03                 |
| Consultation with a paediatric neurologist in the last 12 months   | 1.42 (0.84-2.39)                           | 0.19                 | 1.38 (0.90-2.11)                           | 0.14                 |
| Consultation with a paediatric pneumologist in the last 12 months  | 2.58 (1.53-4.33)                           | <0.001               | 2.47 (1.61-3.77)                           | <0.001               |

**Table 3. Association between bronchopulmonary dysplasia (BPD) and outcomes for very preterm children alive at age 5-6 years. (continued)**

|   | Complete-case<br>N= 1,914                  |                      | Imputed data<br>N= 3,150                   |                      |
|---|--|----------------------|--|----------------------|
|   | BPD<br>N= 248<br>aOR <sup>a</sup> (95% CI) | P-value <sup>b</sup> | BPD<br>N= 394<br>aOR <sup>a</sup> (95% CI) | P-value <sup>b</sup> |
| <b>Healthcare utilisation</b>   |  |                      |  |                      |
| Developmental support <sup>§</sup>  | 1.52 (1.09-2.12)                           | 0.01                 | 1.59 (1.20-2.12)                           | 0.002                |
| Details of the developmental support  |  |                      |  |                      |
| <i>Consultation with psychologist or psychiatrist<sup>h</sup></i>                   | 1.38 (0.95-2.02)                           | 0.09                 | 1.28 (0.93-1.75)                           | 0.13                 |
| <i>Consultation with psychomotor therapist or motor physiotherapist<sup>h</sup></i> | 1.60 (1.12-2.29)                           | 0.01                 | 1.59 (1.18-2.15)                           | 0.002                |
| <i>Consultation with speech therapist<sup>h</sup></i>                               | 1.99 (1.41-2.79)                           | <0.001               | 1.81 (1.34-2.45)                           | <0.001               |
| <i>Consultation with respiratory physiotherapist<sup>h</sup></i>                    | 1.43 (0.64-3.18)                           | 0.38                 | 1.58 (1.05-2.37)                           | 0.03                 |
| <i>Follow-up in rehabilitation centre<sup>h,i</sup></i>                             | 1.02 (0.71-1.47)                           | 0.92                 | 1.11 (0.82-1.51)                           | 0.50                 |
| <i>Any schooling support</i>  | 1.47 (0.96-2.25)                           | 0.08                 | 1.28 (0.89-1.85)                           | 0.18                 |

aOR=adjusted odd ratio; β=adjusted regression coefficient for linear models; CI=confidence interval; GMFCS=Gross Motor Function Classification System; MABC-2=Movement Assessment Battery for Children, 2nd edition; PMA=postmenstrual age; SCQ=Social Communication Score; SDQ=Strengths and Difficulties Questionnaire

<sup>a</sup> Linear models for continuous outcomes, logistic regression models for binomial outcomes, and multinomial regression models for multinomial outcomes. All models were fitted with Generalized Estimating Equations to account for non-independence of outcomes related to multiple births. Reference category for the exposure was children without BPD. The models were multivariable models including the following variables: BPD (binomial) + gestational age (4 categories) + small-for-gestational-age (binomial) + ≥ 1 antenatal corticosteroids course (binomial) + hemodynamic disorders (binomial) + intraventricular hemorrhage (5 categories) + patent ductus arteriosus (binomial) + necrotizing enterocolitis (binomial) + late-onset sepsis (binomial) + extra-uterine growth restriction (3 categories) + maternal educational level (4 categories) + maternal country of birth (5 categories).

<sup>b</sup> Wald-tests.

<sup>c</sup> Includes cerebral palsy, vision, hearing, full-scale intelligence quotient, developmental coordination disorders, and behavioural difficulties.

<sup>d</sup> Cut-off point of the distribution related to the reference group born at term (37-41 weeks).

<sup>e</sup> Among children without cerebral palsy, severe or moderate sensory disabilities, and full-scale intelligence quotient > -2 SD of the distribution related to the reference group born at term.

<sup>f</sup> Full-scale intelligence quotients, measured by the Wechsler Preschool and Primary Scale of Intelligence, 4th edition.

<sup>§</sup> Developmental support was defined as at least two consultations with a psychologist, psychiatrist, orthoptist, speech therapist, psychomotor therapist, physiotherapist, during the last 12 months or schooling in a special school or follow-up in any type of rehabilitation centre.

<sup>h</sup> At least one consultation in the last 12 months.

<sup>i</sup> Any type of rehabilitation centre.

**Figure 1. Flow chart of the study**

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##### **Patient consent for publication**

Assessments occurred only after families had received information and provided written informed consent.

##### **Ethics approval**

This study was approved by the National Data Protection Authority (CNIL DR-2016-290) and by appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, reference No 16.263; Committee for the Protection of People Participating in Biomedical Research, reference 2016- A00333-48).

##### **Data availability statement**

The study protocol, the data access charter and the data access procedure can be found on the EPIPAGE-2 website (<https://epipage2.inserm.fr/index.php/fr/cote-recherche/235-access-aux-donnees-et-questionnaires>). Questionnaires and data catalogues are available on (<https://pandora-epipage2.inserm.fr/public/>).

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