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## **Doxapram for Apnoea of Prematurity and Age 5-6 Years Neurodevelopmental Outcomes**

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**Key words**

Child Development

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**What is already known on this topic**

- Doxapram can be prescribed when apnoea of prematurity persists despite continuous positive airway pressure and optimal caffeine therapy.
- Data on the long-term neurodevelopmental effects of doxapram are controversial.

**What this study adds**

- In a large propensity-score matched study, doxapram treatment for apnoea of prematurity was not associated with age 5-6 years neurodevelopmental disabilities.
- In the short term, treatment with doxapram was not associated with increased mortality.

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

- This study will reassure clinicians about the long-term consequences of doxapram in the treatment of apnoea of prematurity.

## **Abstract**

**Objective** To assess the long-term neurodevelopmental impact of doxapram for treating apnoea of prematurity.

**Design** Secondary analysis of the French national cohort study EIPAGE-2. Recruitment took place in 2011. A standardized neurodevelopmental assessment was performed at age 5-6. A 2:1 propensity-score matching was used to control for the non-randomized assignment of doxapram treatment.

**Setting** Population-based cohort study.

**Patients** All children born before 32 weeks' gestation alive at age 5-6.

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

**Main outcome measures** Neurodevelopmental outcomes at age 5-6 assessed by trained paediatricians and neuropsychologists: cerebral palsy, developmental coordination disorders, intelligence quotient and behavioural difficulties. A composite criterion for overall neurodevelopmental disabilities was built.

**Results:** The population consisted of 2,950 children; 275 (8.6%) received doxapram. Median (interquartile range) gestational age was 29.4 (27.6-30.9) weeks. At age 5-6, complete neurodevelopmental assessment was available for 60.3% (1,780/2,950) of children and partial assessment for 10.6% (314/2,950). In the initial sample, children receiving doxapram had evidence of greater clinical severity than those not treated. Doxapram treatment was associated with overall neurodevelopmental disabilities of any severity (odds ratio 1.43, 95% confidence interval 1.07-1.92,  $p=.02$ ). Eight hundred and twenty-one children were included in the 2:1 matched sample. In this sample, perinatal characteristics of both groups were similar and doxapram treatment was not associated with overall neurodevelopmental disabilities (odds ratio 1.09, 95% confidence interval 0.76-1.57,  $p=.63$ ).

**Conclusions:** In children born before 32 weeks' gestation, doxapram treatment for apnoea of prematurity was not associated with neurodevelopmental disabilities.

## **Introduction**

Apnoea of prematurity (AOP) is common in very preterm children<sup>1</sup> and can lead to chronic hypoxemia and prolonged respiratory support. Two mechanisms may be intertwined: obstructive apnoea and central apnoea. The main treatments are non-invasive ventilatory support (continuous positive airway pressure [CPAP])<sup>1</sup> and the administration of caffeine<sup>1,2</sup>. Nevertheless, for the most immature children, AOP can persist despite CPAP and caffeine administration. Doxapram can be used to try to avoid intubation and invasive mechanical ventilation<sup>3</sup>. Results of 5 randomized clinical trials<sup>4–8</sup> with a small sample size suggested that doxapram might be effective in reducing the occurrence of central AOP. Doxapram acts on the central nervous system by stimulating respiratory centres and increasing minute ventilation tidal volume and mean inspiratory flow<sup>9</sup>. However, one of the main limitations of this treatment is the lack of long-term clinical outcomes reported in those trials and therefore the uncertainty of adverse effects due to the paucity of data reporting. Studies about the neurodevelopmental consequences of doxapram were either retrospective cohort studies whose follow-up ended at 18 to 24 months' corrected age<sup>10</sup> or were case–control studies<sup>11,12</sup> with few children included. In these studies, some neurodevelopmental disabilities secondary to doxapram administration such as an altered mental development index have been reported, but data are contradictory<sup>3</sup>.

The aim of our study was to analyse the long-term neurodevelopmental outcomes after doxapram treatment for AOP in children born before 32 weeks' gestation who were included in a large population-based prospective cohort study.

## **Methods**

### Study design

This is a secondary analysis of the French national population-based and prospective cohort *Etude éPIdémiologique sur les Petits Ages GEstationnels-2* (EPIPAGE-2), with recruitment taking place in 2011. The cohort's protocol<sup>13</sup> and the overall age 5- to 6-year follow-up data<sup>14</sup> have been published. Children born before 32 weeks' gestation and alive at age 5-6 years were eligible for the study.

### Exposure

In France in 2011, in all neonatal intensive care unit, very preterm children were treated at birth with a loading dose of caffeine of 20 mg/kg, followed by a daily maintenance dose. Doxapram was used in addition to caffeine and CPAP in non-intubated children with frequent AOP. The information available for doxapram was administration during the neonatal stay classified as yes/no, date first prescribed, and date last prescribed. Children were classified as "treated" if they received doxapram at any time during the neonatal intensive care unit (NICU) stay. Otherwise, they were classified as "not treated".

### Outcomes

Between age 5 and 6, children included in the EPIPAGE-2 cohort study underwent a standardized paediatric and neuropsychologic assessment. Cerebral palsy was assessed with the Gross Motor Function Classification System (GMFCS)<sup>15</sup> and developmental coordination disorders with the Movement Assessment Battery for Children, second edition<sup>16</sup>. The intelligence quotient (IQ) was scored with the Wechsler Intelligence Scale for Children, fourth edition<sup>17</sup>. Behavioural difficulties were evaluated with the Strengths and Difficulties Questionnaire<sup>18</sup>. To define overall neurodevelopmental disabilities of any severity, we used cerebral palsy grade 1 to 5 according to the GMFCS, cognitive disorders with IQ < -1 SD, visual and hearing impairment, behavioural difficulties and developmental coordination disorders<sup>14</sup>. Moderate and severe overall neurodevelopmental disabilities were defined by

at least one of cerebral palsy  $\geq$  grade 2 according to the GMFCS, IQ  $<$  -2 SDs, bilateral binocular visual acuity  $<$  3.2 and unilateral or bilateral hearing loss  $>$  40 dB<sup>14</sup>.

All test thresholds were calculated from a reference sample of the contemporary French ELFE cohort of term-born children<sup>19</sup>.

### Statistical analyses

The percentage of treated children is described by gestational age. Perinatal characteristics of not-treated and treated children are reported. Among children admitted to the NICU, survival at age 5-6 years was reported according to doxapram treatment status, and bivariable analyses were performed. Pearson's chi-squared test was used for categorical variables and Wilcoxon test for continuous variables. Statistical significance was set at  $P \leq .05$ . All analyses involved using R v4.2.1 (R Core Team).

### *Propensity-score analyses*

A propensity score was built to control for the non-random assignment of the neonates to receive doxapram or not. The propensity score was defined as the child's probability of exposure to doxapram conditional on perinatal characteristics. A logistic regression model was used to calculate the propensity score with doxapram administration as a dependent variable, estimating odds ratios (ORs) and 95% confidence intervals (CIs). All perinatal characteristics known to affect neonatal outcomes were added in the model, including neonatal morbidities that occurred before doxapram administration. A 2:1 matching algorithm without replacement was used to match not-treated and treated children for the propensity score within a caliper of 0.2 SDs of the propensity-score logit<sup>20</sup>. The balance of baseline characteristics in the initial and matched cohort was evaluated. An absolute standardized difference  $<$  10% was considered acceptable<sup>21</sup>. The association between doxapram treatment and neurodevelopmental outcomes was assessed with logistic



regression. To maintain the population-based structure of the EIPAGE-2 cohort, in the initial sample all percentages were weighted on the recruitment period, which depended on the gestational age at birth (weighting factor of 1.0 for children born <27 weeks' gestation and 1.3 for children born at 27-31 weeks' gestation). To assess the association between doxapram and neurodevelopmental outcomes in the most immature children, a subgroup analysis was carried out for children born before 28 weeks' gestation. Because of the few numbers of children receiving doxapram in each centre, this variable was not included in the main propensity score. Nevertheless, we performed a sensitivity analysis including the center in the propensity score with a 1:1 matching algorithm.

#### *Management of children lost to follow-up*

We used multiple imputation by chain equations<sup>22</sup> to account for children lost to follow-up; 50 datasets were imputed with 30 iterations for each (R package MICE<sup>22</sup>). Variables included in the imputation model are detailed in Table S1. All age 5- to 6-year analyses involved imputed data. To assess the impact of multiple imputations on the results of the study, complete-case children were compared to children added in the analyses by multiple imputation.

## **Results**

The study population consisted of 2,950 children alive at age 5-6 years (Figure 1); the median (interquartile range) gestational age at birth was 29.4 (27.6-30.9) weeks. Almost all children received caffeine and 275 (8.6%) received doxapram during the neonatal stay. Median age at onset of treatment decreased from 24 (11-34) days at 24-25 weeks' gestation to 5 (3-9) days at 30-31 weeks' gestation. Median postmenstrual age at onset of treatment were from 28.4 (27.5-29.6) to 31.6 (31.1-32.3) weeks according to gestational age category and that at final discontinuation of treatment was from 30.6 (29.0-32.5) and 33.1

(32.1-34.2) weeks. Further information about doxapram administration by gestational age is in Table 1.

Treatment with doxapram was associated with low gestational age and high respiratory morbidity (Table S2). The rate of children receiving doxapram in each NICU was heterogeneous, ranging from 0 to 40% of children, and 40/116 (34.4%) of the NICUs used doxapram for at least one child. Centres that used doxapram were often level 3 centres and the median gestational age of their patients was lower than those that did not use doxapram (Table S3). Of the 3,646 children admitted to a NICU without congenital malformation, survival at age 5-6 years was similar in the not-treated and treated groups (Table S4).

At age 5-6, complete neurodevelopmental assessment was available for 60.3% (1,780/2,950) of children and partial assessment for 10.6% (314/2,950). The complete-case group and the group added in the analyses by multiple imputation (children lost to follow-up and with only partial assessment) did not differ in gestational age, perinatal characteristics and doxapram treatment rate. However, socioeconomic status was lower in the group added in the analyses (Table S5).

A total of 821 children were matched, 547 in the not-treated group and 274 in the treated group. One child in the treated group was matched with only one child of the not-treated group because of the absence of a second control child. The propensity-score distribution in the initial and matched sample is described in Figure S1. Baseline characteristics of not-treated and treated children in both samples are reported in Table 2. In the initial sample, the treated group had evidence of greater clinical severity (e.g., lower gestational age, lower rate of antenatal corticosteroids, more invasive mechanical ventilation in the first 24 hr) than the not-treated group. In the matched sample, all absolute standardized differences were < 10% (Table 2, Figure S2).

### Initial sample and age 5-6 years outcomes

In the imputed initial sample, 52.7% (95% CI, 50.5-55.0) of children in the not-treated group and 61.5% (95% CI, 54.7-68.3) in the treated group had overall neurodevelopmental disabilities of any severity (Table 3). Moderate to severe overall neurodevelopmental disabilities concerned 46.1% (95% CI, 43.8-48.4) of the not-treated children and 53.1% (95% CI, 46.3-59.8) of the treated children. In a logistic regression model, doxapram treatment was significantly associated with overall neurodevelopmental disabilities of any severity (OR 1.43, 95% CI 1.07-1.92) and with cerebral palsy (OR 1.72, 95% CI 1.08-2.73).

### Matched sample and age 5-6 years outcomes

In the imputed matched sample, 59.7% of children in the not-treated group and 61.9% in the treated group had overall neurodevelopmental disability of any severity at age 5-6 (Table 3). Moderate to severe overall neurodevelopmental disabilities concerned 51.3% of the not-treated children and 53.2% of the treated children. In this sample, doxapram treatment was not associated with overall neurodevelopmental disabilities. Analyses also showed no association between doxapram treatment and cerebral palsy, developmental coordination, full-scale IQ < -1 SD and -2 SDs and behavioural difficulties (Table 3).

### Subgroup analyses: 2:1 matching in children born $\leq$ 28 weeks' gestation

Subgroup analyses of children born before 28 weeks' gestation concerned 1,220 children in the initial sample and 649 children in matched analyses. Doxapram treatment was not associated with neurodevelopmental disabilities in the initial sample or the matched sample (Table S6).

### Sensitivity analyses: 1:1 matching including the center in the propensity-score

In the 1:1 sample matched on a propensity score that included the centre (438 children analysed), doxapram treatment was not associated with neurodevelopmental disabilities (Table S7).

## **Discussion**

The long-term effects of treatments are crucial in neonatology, and many of those used have not been found safe in the short or long term. In this large propensity-score matched study, we found no evidence that doxapram treatment for AOP is associated with long-term neurodevelopmental disabilities.

In children with persistent AOP despite optimal CPAP level and caffeine treatment, doxapram has been suggested as second-line treatment to avoid invasive mechanical ventilation. However, there are many uncertainties about the long-term benefit/risk ratio of this treatment: on one hand, doxapram treatment might decrease AOP and mechanical invasive ventilation, which are strongly associated with neurodevelopmental disabilities<sup>23,24</sup>, and on the other, this treatment with neurological short-term effects may also have long-term adverse effects on the developing brain. For example, in an observational study of preterm children, doxapram was associated with increased electrographic seizure activity and decreased sleep-wake cycling<sup>25</sup>.

Published studies<sup>3,10-12</sup> with neurodevelopmental assessment are contradictory and have limited high-quality evidence. In our initial sample, doxapram treatment was associated with disabilities but with a major risk of allocation bias. Indeed, the most immature children often received doxapram but were also those the most at risk of neurodevelopmental complications. After matching on a propensity score to control for this allocation bias, the perinatal characteristics of the not-treated and treated groups were similar, with no longer an association between doxapram treatment and age 5-6 years neurodevelopmental

disabilities. This finding is important for clinicians who face a dilemma when AOP persists despite CPAP and optimal caffeine treatment: administer mechanical invasive ventilation and sedation, whose deleterious effects on neurodevelopment are suspected<sup>26,27</sup>, or try adding doxapram treatment with unknown long-term adverse effects. Our study might reassure clinicians about the long-term neurodevelopmental consequences of doxapram and might help to harmonize practices that are for the time being clearly heterogeneous among NICUs. Finally, we could have expected treatment with doxapram to be associated with a decrease in neurodevelopmental disabilities via a decrease in AOP, but this effect, if it exists, is probably too indirect to be demonstrated or would require a larger number of treated children.

Our study has several strengths. The first is the age of the neurodevelopmental assessment. To our knowledge, this is the first work to evaluate the potential impact on neurodevelopment of doxapram at age 5-6 years in very preterm children. The second strength is the quality of the neurodevelopmental evaluation. Each child was assessed in a standardized way by trained paediatricians and a neuropsychologist and many areas of neurodevelopment were covered. Finally, with 275 children born before 32 weeks' gestation treated, this is the largest study of the neurodevelopmental long-term impact of doxapram to date.

The study does have limitations. First, the risk of allocation bias is high when studying the impact of treatments in observational studies. However, by creating study groups with similar characteristics, the propensity-score matching approach is the best way to reduce this risk as much as possible<sup>28</sup>. Furthermore, with the extended data collection from the antenatal period in the EIPAGE-2 cohort, we could include in the propensity score the main known perinatal characteristics of children that may affect the decision to treat with

doxapram. The second limitation was the follow-up rate at age 5-6 years. Complete neurodevelopmental assessment was available for only 60.3% (1,780/2,950) of children and partial assessment for 10.6% (314/2,950). However, this is a usual follow-up rate in very preterm children.<sup>29</sup> In addition, as the loss to follow-up in very preterm cohorts depends on socio-economic conditions, we performed multiple imputations to account for attrition bias.<sup>29</sup> We also compared complete-case children to those included by multiple imputations and found no difference in the doxapram treatment rate. The third limitation is the lack of detail on the administration of doxapram. We did not have the dose administered or whether doxapram was given intravenously or via gastric tubes. However, in a 2005 survey of practice in France, the mean dosage for doxapram in AOP treatment was initially 0.6 mg/kg/hr intravenously with an increase to a maximum of 1.4 mg/kg/hr,<sup>30</sup> which agreed with common international practice.<sup>3</sup>

We did not attempt to evaluate the efficacy of doxapram or the short-term adverse effects. Our data were too imprecise to assess efficacy. For short-term adverse effects, we had no data on hypokalaemia, arterial hypertension or the time between the start of treatment with doxapram and digestive morbidities such as necrotizing enterocolitis, although these are the most frequently reported potential adverse effects of doxapram<sup>3</sup>. Because neurodevelopmental follow-up is the added value of our large population-based cohort study of very preterm children as compared with the published randomized trials, we chose to focus on the long-term neurodevelopmental impact of this treatment, for which there are very few data. Finally, before using doxapram, clinicians must consider the possible short- and long-term complications of this drug in order to assess its benefit/risk balance. Some data also suggest that dosing should be adapted to the gestational age and the postnatal age

of the patient to decrease the risk of adverse event.<sup>31</sup> The DOXA-Trial currently underway will probably provide some new data on this treatment.<sup>32</sup>

### **Conclusions**

In a large prospective propensity-score matched study, doxapram treatment for AOP was not associated with neurodevelopmental disabilities at age 5-6 years in children born before 32 weeks' gestation. This treatment was also not associated with an increase in mortality for children admitted to a NICU. Nevertheless, future studies are needed to conclude definitively on the benefit/risk balance of this drug for treating AOP.

**Table 1. Baseline characteristics of doxapram administration in children by gestational age**

	Gestational age					p <sup>a</sup>
	24-25 weeks N= 224	26-27 weeks N= 607	28-29 weeks N= 841	30-31 weeks N= 1,278	Total N= 2,950	
Caffeine, <sup>b</sup> n/N (% <sup>c</sup> )	224/224 (100.0)	606/607 (99.8)	840/840 (100.0)	1,257/1,277 (98.4)	2,927/2,948 (99.3)	<.001
Doxapram, n/N (% <sup>c</sup> )	58/224 (25.9)	113/607 (17.9)	79/841 (9.4)	25/1,278 (2.0)	275/2,950 (8.6)	<.001
Detailed information on treatment with doxapram:						
Total treatment time (days), median (IQR)	14 (4-24)	13 (6-20)	8 (3-21)	5 (3-17)	10 (4-20)	<.001
Age at onset of treatment (days), median (IQR)	24 (11-34)	13 (6-18)	9 (3-13)	5 (3-10)	11 (5-17)	<.001
PMA at onset of treatment (weeks), median (IQR)	28.7 (26.9-30.0)	28.4 (27.7-29.9)	30.0 (29.4-30.6)	31.6 (31.2-32.4)	29.6 (28.3-30.7)	<.001
Age at final discontinuation of treatment (day), median (IQR)	37 (25-53)	26 (18-38)	19 (12-35)	15 (8-27)	25 (15-37)	<.001
PMA at final discontinuation of treatment (weeks), median (IQR)	30.6 (29.0-32.5)	30.6 (29.6-32.5)	31.3 (30.5-33.6)	33.1 (32.1-34.3)	31.1 (30.0-33.3)	<.001

PMA=postmenstrual age; IQR=interquartile range

In each column of the table, the denominators may vary due to missing data.

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

<sup>b</sup> Caffeine treatment was started on Day 0 with a loading dose of 20 mg/kg and then continued with a daily maintenance dose. All children that received doxapram received caffeine first.

<sup>c</sup> All percentages were weighted on the recruitment period, which depended on the gestational age (weighting factor 1.3 for children born at 27-31 weeks' gestation).



**Table 2. Baseline characteristics of the population after imputation and matching**

	Population study after multiple imputation N= 2,950					
	Initial sample, % (95% CI) <sup>a</sup>			2:1 matched sample, %		
	Not treated (n=2,675)	Treated (n= 275)	SD (%)	Not treated (n= 547)	Treated (n= 274)	SD (%)
<b>Perinatal characteristics included in the propensity score</b>						
Boy	52.1 (50.2-54.0)	55.8 (49.9-61.7)	6.5	54.6	55.2	1.1
Gestational age (weeks)						
24-25	4.8 (4.1-5.5)	17.8 (13.5-22.0)	36.5	19.9	21.0	2.0
26-27	16.9 (15.5-18.3)	39.3 (33.5-45.1)	46.0	42.1	41.1	1.9
28-29	29.6 (27.9-31.4)	32.6 (26.8-38.4)	0.5	28.9	28.8	0.01
30-31	48.7 (46.8-50.6)	10.3 (6.5-14.1)	131.3	9.1	9.1	0.4
Maternal age (y)						
< 25	18.8 (17.3-20.3)	19.9 (15.2-24.7)	2.9	20.1	19.9	0.9
25-35	63.1 (61.3-64.9)	64.5 (58.8-70.3)	3.3	63.6	64.8	2.6
> 25	18.1 (16.7-19.6)	15.5 (11.1-19.9)	7.7	16.3	15.3	2.5
Primiparous	40.9 (38.0-43.7)	38.2 (31.0-45.4)	6.8	61.2	62.2	1.9
Multiple birth	32.4 (30.6-34.2)	36.7 (30.9-42.4)	9.2	35.7	36.6	1.8
Small-for-gestational-age <sup>b</sup>	35.6 (33.8-37.5)	25.3 (20.0-30.6)	25.9	23.6	24.1	1.1
≥ 1 antenatal corticosteroids course	68.1 (66.3-69.9)	60.1 (54.2-66.1)	15.6	60.1	60.5	1.2
Antenatal magnesium sulphate	9.3 (8.2-10.4)	4.8 (2.2-7.3)	20.5	4.7	4.9	1.0
Cause of preterm birth						
Preterm labour	35.1 (26.1-43.7)	46.0 (33.1-58.9)	22.8	47.0	46.9	0.6
PROM	25.1 (22.6-27.5)	24.7 (18.8-30.7)	0.01	25.3	25.3	0.3
Hypertensive disorders	30.4 (21.4-39.4)	22.0 (10.6-33.3)	21.9	21.1	21.1	0.2
Others	9.4 (7.7-11.2)	7.3 (3.2-11.3)	10.7	6.6	6.7	0.3
Inborn status	87.3 (86.1-88.6)	83.8 (79.3-88.2)	9.0	84.8	84.1	0.2
Caesarean section	67.5 (65.7-69.2)	58.9 (53.0-64.8)	17.8	58.1	58.1	1.5
Apgar score ≤ 7 at 5 min after birth	26.1 (24.4-27.8)	39.5 (33.5-45.4)	27.8	39.2	40.1	1.3
Surfactant administration	61.6 (59.7-63.5)	84.6 (80.2-89.1)	65.6	87.3	85.8	4.6
Non-invasive ventilation in the first 24 hr	72.5 (70.8-74.2)	48.0 (42.0-54.0)	49.3	46.5	46.5	0.5
Caffeine administration	99.2 (98.8-99.5)	100.0 (100.0-100.0)	9.3	100.0	100.0	0.0

**Table 2. Baseline characteristics of the population after imputation and matching (continued)**

	Population study after multiple imputation N= 2,950					
	Initial sample, % (95% CI) <sup>a</sup>			2:1 matched sample, %		
	Not treated (n=2,675)	Treated (n= 275)	SD (%)	Not treated (n= 547)	Treated (n= 274)	SD (%)
IVH <sup>c</sup> before day 7						
No IVH	79.6 (78.1-81.2)	78.7 (73.8-83.5)	3.0	77.0	77.7	1.5
Low-grade IVH	18.6 (17.2-20.1)	20.0 (15.3-24.8)	4.2	21.5	20.9	1.3
High-grade IVH	1.7 (1.2-2.2)	1.3 (0.0-2.6)	4.0	1.5	1.4	0.9
Necrotizing enterocolitis <sup>d</sup> before day 7	0.3 (0.1-0.5)	0.4 (0.00-1.1)	1.7	0.3	0.4	0.6
Late-onset sepsis <sup>e</sup> before day 7	3.7 (3.0-4.4)	5.9 (3.1-8.7)	8.8	6.3	6.0	1.5
Maternal educational level						
< Secondary school	33.9 (32.0-35.8)	34.9 (29.0-40.7)	1.5	34.7	34.5	0.6
Secondary school	21.5 (19.9-23.1)	21.4 (16.3-26.4)	1.1	21.1	21.1	0.1
1 or 2 years post-secondary school	19.4 (17.8-20.9)	18.3 (13.6-23.0)	1.4	18.5	18.9	1.3
≥ 3 years post-secondary school	25.2 (23.5-26.9)	25.4 (20.2-30.7)	0.6	25.7	25.5	0.4
Maternal country of birth						
France	75.2 (73.5-76.8)	80.2 (75.4-85.0)	12.4	80.7	80.0	1.6
Other European country	2.5 (1.9-3.1)	5.2 (2.4-7.9)	10.6	4.2	4.8	2.3
North Africa country	8.6 (7.5-9.7)	7.7 (4.5-10.9)	2.9	7.9	7.8	0.3
Other African country	7.9 (6.9-9.0)	5.1 (2.6-7.6)	11.1	5.6	5.6	0.2
Other	5.8 (4.9-6.7)	1.8 (0.2-3.4)	29.0	1.6	1.9	1.9

CI=confidence intervals; IVH=intraventricular haemorrhage; PMA= postmenstrual age; PROM=preterm rupture of membranes; SD=standardized difference

<sup>a</sup> In the initial sample, all percentages were weighted on the recruitment period, which depended on the gestational age (weighting factor 1.3 for children born at 27-31 weeks' gestation).

<sup>b</sup> Small-for-gestational-age was defined as birth weight less than the 10<sup>th</sup> centile for gestational age and sex based on French intrauterine growth curves (*Ego et al. 2016*).

<sup>c</sup> IVH was defined with the Papile classification system (*Papile et al. 1978*). Grades 1 and 2 IVH were classified as low-grade IVH. Grades 3 and 4 IVH were classified as high-grade IVH.

<sup>d</sup> Necrotizing enterocolitis corresponded to grade ≥ 2 of the Bell classification (*Bell et al. 1978*).

<sup>e</sup> Late-onset sepsis was defined as a positive blood culture after 72 hr of life, associated with antibiotic administration for ≥5 days, or death within 5 days after a positive blood culture.

**Table 3. Age 5-6 years neurodevelopmental outcomes of the population after imputation and matching**

	Population study after multiple imputations N= 2,950					
	Initial sample		Matched sample 2:1			
	% (95% CI) <sup>a</sup>		%		OR (95% CI)	P
	Not treated (n=2,675)	Treated (n= 275)	Not treated (n= 547)	Treated (n= 274)		
<b>Age 5-6 years neurodevelopmental outcomes</b>						
Overall cerebral palsy <sup>b</sup>	6.4 (5.3-7.5)	10.6 (6.5-14.6)	10.2	10.8	1.06 (0.62-1.83)	.83
Developmental coordination disorders (N= 1,434) <sup>c</sup>						
Total MABC-2 score ≤ 5 <sup>th</sup> centile <sup>d</sup>	8.8 (7.3-10.2)	11.8 (6.6-17.1)	13.1	12.1	0.95 (0.62-1.45)	.80
Full-scale IQ						
Total WPPSI score ≤ -1 SD (93) <sup>d</sup>	40.7 (38.4-43.0)	47.5 (40.2-54.8)	45.1	48.0	1.12 (0.77-1.63)	.54
Total WPPSI score ≤ -2 SD (79) <sup>d</sup>	14.9 (13.1-16.7)	15.5 (10.2-20.8)	17.8	16.1	0.88 (0.55-1.39)	.57
Behavioural difficulties						
Total SDQ score ≥ 90 <sup>th</sup> centile <sup>d</sup>	11.0 (9.6-12.5)	12.2 (7.4-17.0)	11.9	12.2	1.03 (0.57-1.85)	.93
Overall neurodevelopmental disabilities <sup>e</sup>						
Overall neurodevelopmental disabilities of any severity	52.7 (50.5-55.0)	61.5 (54.7-68.3)	59.7	61.9	1.09 (0.76-1.57)	.63
Moderate and severe overall neurodevelopmental disabilities	46.1 (43.8-48.4)	53.1 (46.3-59.8)	51.3	53.2	1.08 (0.75-1.55)	.67

IQ=intelligence quotient; CI= confidence interval; MABC-2= Movement Assessment Battery for Children, 2nd edition; OR= odds ratio; SD, standardized difference; SDQ= *Strength* and Difficulties Questionnaire; WPPSI= Wechsler Preschool and Primary Scale of Intelligence

All models were crude logistic regressions and p-values were calculated with Wald tests.

<sup>a</sup> In the initial sample, all percentages were weighted on the recruitment period, which depended on the gestational age (weighting factor 1.3 for children born at 27-31 weeks' gestation).

<sup>b</sup> Cerebral palsy was defined by Gross Motor Functional Classification System 1-5.

<sup>c</sup> Among children without cerebral palsy, severe or moderate sensory disabilities, and with full-scale IQ > -2 SDs of the distribution related to the reference group born at term

<sup>d</sup> Cut-off point of the distribution related to the reference group of term-born children from the Étude Longitudinale Française depuis l'Enfance (ELFE) cohort assessed with the EPIPAGE-2 follow-up protocol.

<sup>e</sup> Grade 1 to 5 cerebral palsy, cognitive disorders with IQ < -1 SD, visual and hearing impairment, behavioural difficulties and developmental coordination disorders were used to define overall neurodevelopmental disabilities of any severity. Moderate and severe overall neurodevelopmental disabilities were defined by at least one of cerebral palsy ≥ grade 2, IQ < -2 SDs, bilateral binocular visual acuity <3.2 and unilateral or bilateral hearing loss > 40 dB.

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

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### **Ethics statements**

#### **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-acces-aux-donnees-et-questionnaires>). Questionnaires and data catalogues are available on (<https://pandora-epipage2.inserm.fr/public/>).

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