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ORIGINAL ARTICLE

Treating very preterm European infants with inhaled nitric oxide increased in-hospital mortality but did not affect neurodevelopment at 5 years of age

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Abstract

Aim: We examined the outcomes of using inhaled nitric oxide (iNO) to treat very preterm born (VPT) infants across Europe.

Methods: This was a sub-study of the Screening to Improve Health in Very Preterm Infants in Europe research. It focused on all infants born between 22+0 and 31+6 weeks/days of gestation from 2011 to 2012, in 19 regions in 11 European countries. We studied 7268 infants admitted to neonatal care and 5 years later, we followed up the outcomes of 103 who had received iNO treatment. They were compared with 3502 propensity score-matched controls of the same age who did not receive treatment.

Results: All countries used iNO and 292/7268 (4.0%) infants received this treatment, ranging from 1.2% in the UK to 10.5% in France. There were also large regional variations within some countries. Infants treated with iNO faced higher in-hospital mortality than matched controls (odds ratio 2.03, 95% confidence interval 1.33–3.09). The 5-year follow-up analysis of 103 survivors showed no increased risk of neurodevelopmental impairment after iNO treatment.

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; EPICE, Effective Perinatal Intensive Care in Europe; GA, gestational age; iNO, inhaled nitric oxide; IQR, interquartile range; NICU, neonatal intensive care unit; OR, odds ratio; PPHN, persistent pulmonary hypertension of the newborn; pPROM, prolonged premature rupture of membranes; SD, standard deviation; SGA, small for gestational age; SHIPS, Screening to Improve Health in Very Preterm Infants; SMD, standardised mean differences; VPT, very preterm.

The Screening to Improve Health in Very Preterm Infants in Europe (SHIPS) Research Group: A complete list of group members appears in Appendix S1.

Conclusion: iNO was used for VPT patients in all 11 countries. In-hospital mortality was increased in infants treated with iNO, but long-term neurodevelopmental outcomes were not affected in 103 5-year-old survivors.

KEYWORDS
European study, inhaled nitric oxide, mortality, neurodevelopment, very preterm infants

1 | INTRODUCTION

Inhaled nitric oxygen (iNO) is a well-established treatment for improving oxygenation in infants who are born at full term. It has been shown to reduce the overall burden of disease in these patients.[1,2] The indications for using iNO in neonatal intensive care units (NICUs) are mainly rescue therapy for refractory hypoxemia and severe persistent pulmonary hypertension of the newborn (PPHN). The prevalence of PPHN has increased in neonates. The diverse reasons for this include clinical chorioamnionitis, prolonged premature rupture of membranes (pPROM)[3] and severe respiratory distress syndrome, leading to recurrent hypoxia.[4]

There is an ongoing debate about using iNO for preterm infants. A large European trial published in 2020 was inconclusive about using iNO to prevent bronchopulmonary dysplasia (BPD) in premature infants with respiratory distress. It reported that iNO did not result in either long-term benefits or adverse long-term sequelae.[5] In addition, iNO was not mentioned in the 2022 update to the European Consensus Guidelines on the Management of respiratory distress syndrome.[6] On the other hand, several American organisations have stated that iNO is superior to other pulmonary vasodilators used to treat preterm infants with severe pulmonary hypertension. The statements from The American Heart Association, the American Thoracic Society in 2015[7] and the Paediatric Pulmonary Hypertension Network in 2016[8] empowered its use. Moreover, a review published in 2020 concluded that there was no evidence that using iNO for preterm infants was harmful and suggested that the practice was likely to be safe.[9] However, another study published in 2018 associated iNO exposure with higher mortality among preterm neonates who had respiratory distress syndrome that was not accompanied by PPHN.[10]

To our knowledge, there have not been any long-term, follow-up studies on using iNO for very preterm (VPT) infants when they reached 5 years of age. Studies with shorter follow-up periods have variously shown worsened, better or unchanged neurodevelopmental outcomes following iNO.[11–14]

The main aim of this European study was to report the in-hospital mortality rates and 5-year neurodevelopmental outcomes of VPT infants exposed to iNO in NICUs. Our secondary aim was to investigate the overall use of iNO in the 11 European countries that participated.

Key Notes

- This study examined the outcomes of using inhaled nitric oxide (iNO) to treat very preterm born (VPT) infants in 19 regions in 11 countries across Europe.
- A total of 292 (4.0%) infants received iNO, ranging from 1.2% in the UK to 10.5% in France, and there were also large regional variations within some countries.
- In-hospital mortality was increased, but long-term neurodevelopmental outcomes were not affected in 103 five-year-old survivors.

2 | METHODS

2.1 | Study cohort

The data were collected from two linked studies that followed up area-based cohorts of children from 19 regions in 11 European countries: Belgium, Denmark, Estonia, France, Germany, Italy, the Netherlands, Poland, Portugal, the UK and Sweden. The first was the original Effective Perinatal Intensive Care in Europe (EPICE) study and the second was the follow-up Screening to Improve Health in Very Preterm Infants prospective cohort study (SHIPS). The original EPICE cohort comprised all 10 329 infants born between 22 + 0 and 31 + 6 weeks of gestation. Participating regions started data collection between March and July 2011 and the inclusion period lasted 12 months, except for in France, where it was 6 months. Regions were selected with respect to geographic and organisational diversity and feasibility. This meant they already had systems for collecting population-based data on VPT babies that could be modified and integrated into our study protocol.[15,16] Investigators in each region abstracted data from the medical records in obstetric and neonatal units.

Infants who were admitted to NICUs within 24 h of birth were included in this study. There were missing data on iNO exposure for 368 infants and another one died. The final study sample comprised 7268 infants.

The current study focused on 292 children (4.0%) who had received iNO during the neonatal period. We found that 284 of these had good 1:1 matches and they were selected for further analysis so

that we could compare them with untreated infants. In 2016–2018, when the children were 5 years of age, the families were invited to participate in a comprehensive follow-up study that was based on a parental questionnaire. We were able to gather follow-up data on 103 of the 178 infants who survived to discharge (Figure 1). Only a small number of infants died between discharge and the 5-year follow-up: 6 (3.4%) were treated with iNO and 25 (0.4%) were not. A previous study showed that the missing cases that were lost to follow up were mainly children from families with lower socioeconomic status and there were few differences in clinical characersitics.[16]

The main exposure of this study was treatment with iNO, but the exact timing and duration of iNO were not recorded.

The primary outcome of this study was in-hospital mortality and neurodevelopmental outcomes. Information on survival was abstracted from the medical records. A parental questionnaire explored the neurodevelopmental outcomes, such as cerebral palsy, hearing impairment, motor impairment, speech delay and vision impairment at the 5-year follow-up point.[16] The questionnaire comprised four choice items to assess neurosensory impairments: vision, hearing, fine and gross motor skills. These were based on standard definitions for classifying neurodevelopmental disabilities in preterm populations and adapted for children at 5 years of age.[17] The questionnaire also asked for information on any diagnoses of cerebral palsy and the choice was yes or no. The questionnaire was piloted in English with parents recruited through the European Foundation for the Care of Newborn Infants. The final translated versions were pretested in various countries by parents with 5-year-old children.

Our secondary outcome was the use of iNO in the different regions and countries in the study group.

2.2 | Statistics

The data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous data, as appropriate. The data for categorical variables are presented as numbers and percentages. Groupwise differences were tested using the Student's *t*-test. iNO exposure was not randomly assigned in this prospective cohort. We used propensity score matching to reduce the imbalance of the measured baseline characteristics between the patients who

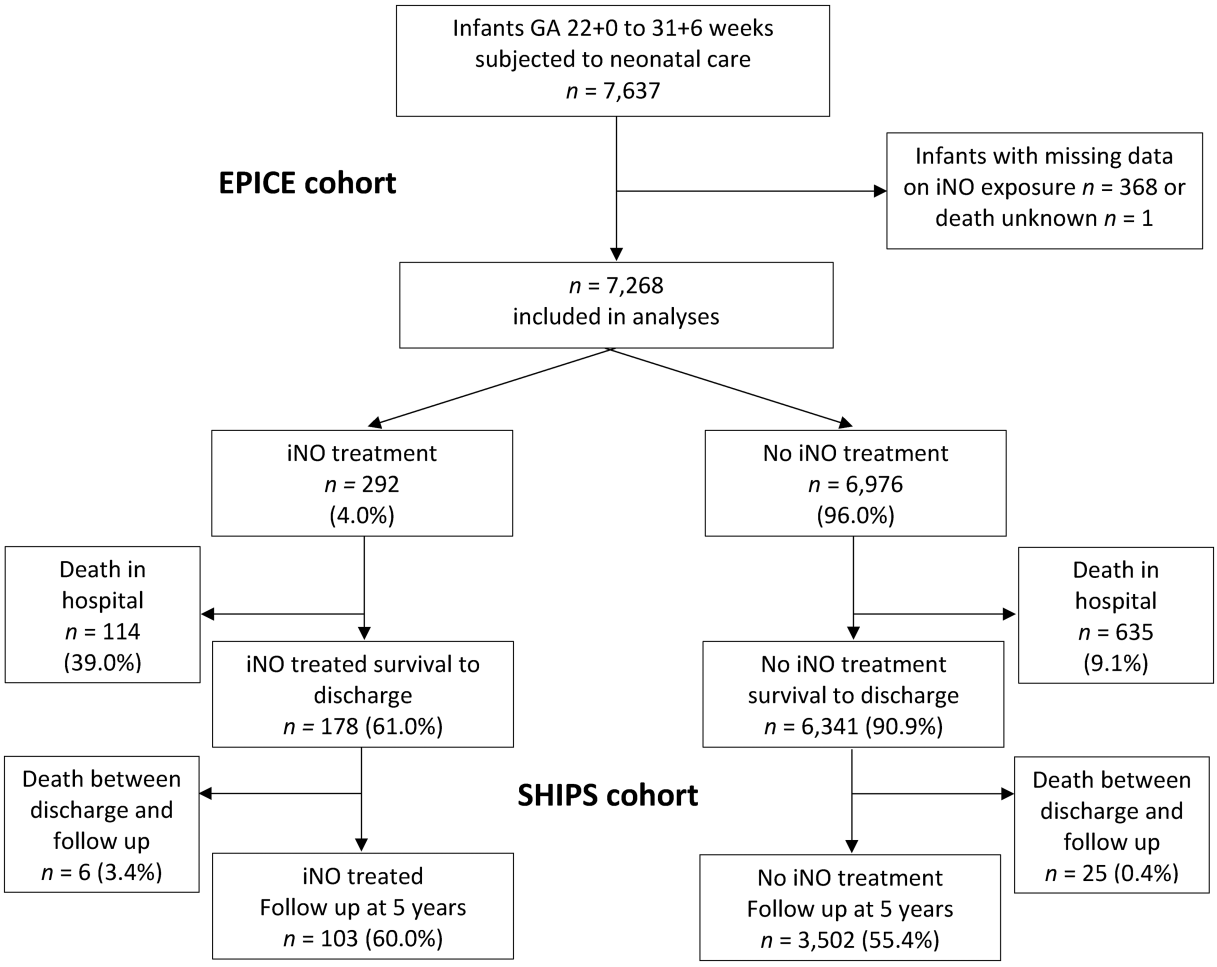

FIGURE 1 Flow chart of inclusions and exclusions and iNO treatment in the original EPICE cohort and in the follow-up SHIPS cohort at 5 years of age. The final study sample comprised 7268 infants born very preterm (22 + 0 to 31 + 6 weeks of gestation) in Europe and 292 were treated with iNO. Loss to follow-up at 5 years mainly consisted of children from families with lower socioeconomic status. iNO, inhaled nitric oxide; *n*, numbers.

received iNO and their matched controls. This process used a ratio of 1:1 and a calliper width of 0.2. The baseline characteristics included maternal age, multiple pregnancies, region and country, antepartum haemorrhage, premature contractions, eclampsia, administration of antenatal corticosteroids, infections prompting delivery and mode of delivery. They also included pPROM, defined as rupture of the membranes more than 12 h before the onset of labour during the actual pregnancy. The infant-related factors included gestational age, sex, birth weight and small for gestational age, defined as a birth weight of <3rd percentile for gestational age according to customised intrauterine growth curves. They also included the infants' Apgar scores, any early onset infection before 72 h, the number of surfactant doses they received and any use of mechanical ventilation. These were all used as independent variables in a logistic regression model that predicted the assignment of iNO treatment and was used to compute the propensity scores (Table 1). Goodness of match is presented in Figure 2. The covariate balance before and after matching was determined using the standardised mean difference.

There were missing data for several of the examined covariates (Table S1). Multiple imputations with chained equations were used to impute missing data and this generated 10 separate imputed data sets.[18] Propensity score matching and statistical modelling were performed for each of the imputed datasets. We subsequently pooled the resulting regression coefficients and their standard errors to compute the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between iNO therapy and each of the investigated outcomes.

We set the significance threshold at $p=0.05$. The statistical analysis was performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Groupwise differences in the odds of survival were assessed using logistic regression. The results are presented using odds ratios (ORs) and their 95% confidence intervals (CIs). To examine the heterogeneity of the treatment effect, we performed similar analyses in pre-specified subgroups in the study population. These were pPROM in infants born at <28 weeks or ≥28 weeks, deliveries prompted by infections and deliveries by Caesarean section. Due to the lack of power, these subgroup analyses were merely exploratory (Table S2).

We also examined the odds of cerebral palsy, vision impairment, hearing impairment, motor impairment and speech delays at 5 years of age. Children were classified as having no, mild, moderate or severe neurodevelopmental impairment, based on the responses to the parental questionnaire.[16] The Kaplan–Meier method was used to estimate survival probabilities over time for all study participants, within each of the 10 imputed datasets.

2.3 | Ethics

All the study regions obtained ethical approval in line with their own national legislation. The EPICE study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (number 13.020). The SHIPS study was approved by the French Expert Committee for Research, Studies and Evaluations in the field of Health (number 12460bis). The French National Commission for Data Protection and Liberties approved both the EPICE (DR-2013-194) and SHIPS (DR-2018-093) studies. Parents provided written informed consent before the families participated in the follow-up study and before any data were collected. Databases in some of the regions contained information for children who died during hospitalisation.

3 | RESULTS

3.1 | Demographics

The total study sample comprised 7268 infants, (54.0% male) born at a median (IQR) gestational age of 29.6 (27.6–31.0) weeks and a median (IQR) birth weight of 1200 (920–1495) grams. Of these, 2146 (29.5%) were born at <28 weeks and 5122 (70.5%) between 28 + 0 and 31 + 6 weeks of gestation. The total incidence of iNO treatment was 4.0% for the whole cohort: 8.4% for infants born at <28 weeks and 2.2% for infants born between 28 + 0 and 31 + 6 weeks of gestation. Patients who were treated with iNO had a lower gestational age and birth weight than patients who did not receive iNO treatment (Table 1). We also observed that some prenatal risk factors were more prevalent in the iNO group, such as pPROM, antepartum haemorrhage and prenatal infections that prompted delivery. Moreover, we found that patients treated with iNO had lower Apgar scores and received a greater number of surfactant doses. They were also more likely to suffer early infections and require mechanical ventilation than the controls. However, we did not observe any significant differences in any of the examined covariates after propensity score matching (Table 1).

3.2 | Variations in iNO treatment between countries and regions

iNO was used in all the cohorts in the 19 regions of the 11 participating countries. A total of 292/7268 (4.0%) VPT infants received iNO, ranging from 1.2% in the UK to 10.5% in France (Figure 3). There were large variations within countries. In Portugal, for example, 4.4% of the VPT infants received iNO in Lisbon, but none of them received it in the northern regions.

3.3 | iNO treatment and patient outcomes

The mortality rate at discharge was higher in the iNO group than in the matched control group (OR 2.03, 95% CI 1.33–3.09). The mortality rate was greatest in the first 2 weeks after birth in both groups (Figure 4).

We followed up with 103/172 (60.0%) of the children who received iNO treatment and were alive when they were 5 years of age, to assess whether they had neurodevelopmental impairment as a result of that

TABLE 1 Baseline characteristics before and after propensity score matching.

	Unmatched			Matched		
	No iNO treatment ($n = 6976$)	iNO treatment ($n = 292$)	SMD	No iNO treatment ($n = 284$)	iNO treatment ($n = 284$)	SMD
Maternal and pregnancy characteristics						
Maternal age, years, mean (SD)	30.5 (6.0)	30.6 (5.7)	0.01	30.1 (5.9)	30.5 (5.8)	0.07
Multiple pregnancies	2219 (31.8%)	83 (28.4%)	0.07	84 (29.6%)	83 (29.2%)	0.01
pPROM	1662 (24.1%)	125 (43.6%)*	0.42	125(44.0%)	124 (43.7%)	0.01
Antepartum haemorrhage	1383 (20.2%)	75 (26.5%)*	0.15	74 (26.1%)	75 (26.4%)	0.01
Premature contractions	3378 (49.2%)	122 (43.0%)	0.13	123 (43.4%)	122 (43.0%)	0.01
Eclampsia	1055 (15.3%)	42 (14.6%)	0.02	38 (13.4%)	41 (14.4%)	0.03
Antenatal corticosteroids	6119 (88.5%)	259 (88.7%)	0.01	249 (87.7%)	251 (88.4%)	0.02
Infection prompted delivery	589 (9.0%)	49 (18.4%)*	0.28	54 (19.0%)	55 (19.4%)	0.01
Caesarean section	4660 (67.3%)	208 (71.7%)	0.13	205 (72.2%)	203 (71.5%)	0.02
Spontaneous onset of delivery	3902 (56.4%)	160 (55.0%)	0.03	151 (53.2%)	251 (88.4%)	0.02
Infant birth characteristics						
GA, weeks	29.7 (27.6–31.0)	27.1 (25.4–29.1)*	0.81	27.0 (25.4–28.7)	27.1 (25.4–29.1)	0.06
Male sex, *n* (%)	3768 (54.0%)	161 (55.1%)	0.02	163 (57.4%)	157 (55.3%)	0.04
Birth weight, g (SD)	1226 (386)	984 (405)*	0.60	950 (385)	987 (406)	0.09
Small for gestational age[a]	1435 (20.6%)	66 (22.6%)	0.05	79 (27.8%)	64 (22.5%)	0.12
Infant characteristics						
Apgar score at 5 min	8 (7–9)	7 (6–8)*	0.60	7 (5–8)	7 (6–8)	0.07
Early infection	427 (6.9%)	42 (18.7%)*	0.40	68 (23.9%)	75 (26.4%)	0.06
Surfactant, doses (*n*)	1 (0–1)	2 (1–2)*	1.04	2 (1–2)	2 (1–2)	0.01
Mechanical ventilation	4042 (58.2%)	284 (97.3%)*	1.066	273 (96.1%)	276 (97.2%)	0.06

Note: Data are medians (IQRs) and/or percentages. There were 7268 infants born at 22 + 0 to 31 + 6 weeks gestation. Imputation of data in both the matched and the unmatched cohort was performed.

Abbreviations: GA, gestational age; pPROM, preterm premature rupture of membranes; SMD, standardised mean difference.

[a]Defined as a birth weight < 3rd percentile for gestational age, according to customised intrauterine growth curves (Ludvigsson et al 2018).

*Shows significant differences between treated and untreated infants in the entire cohort *t*-test ($p < 0.05$).

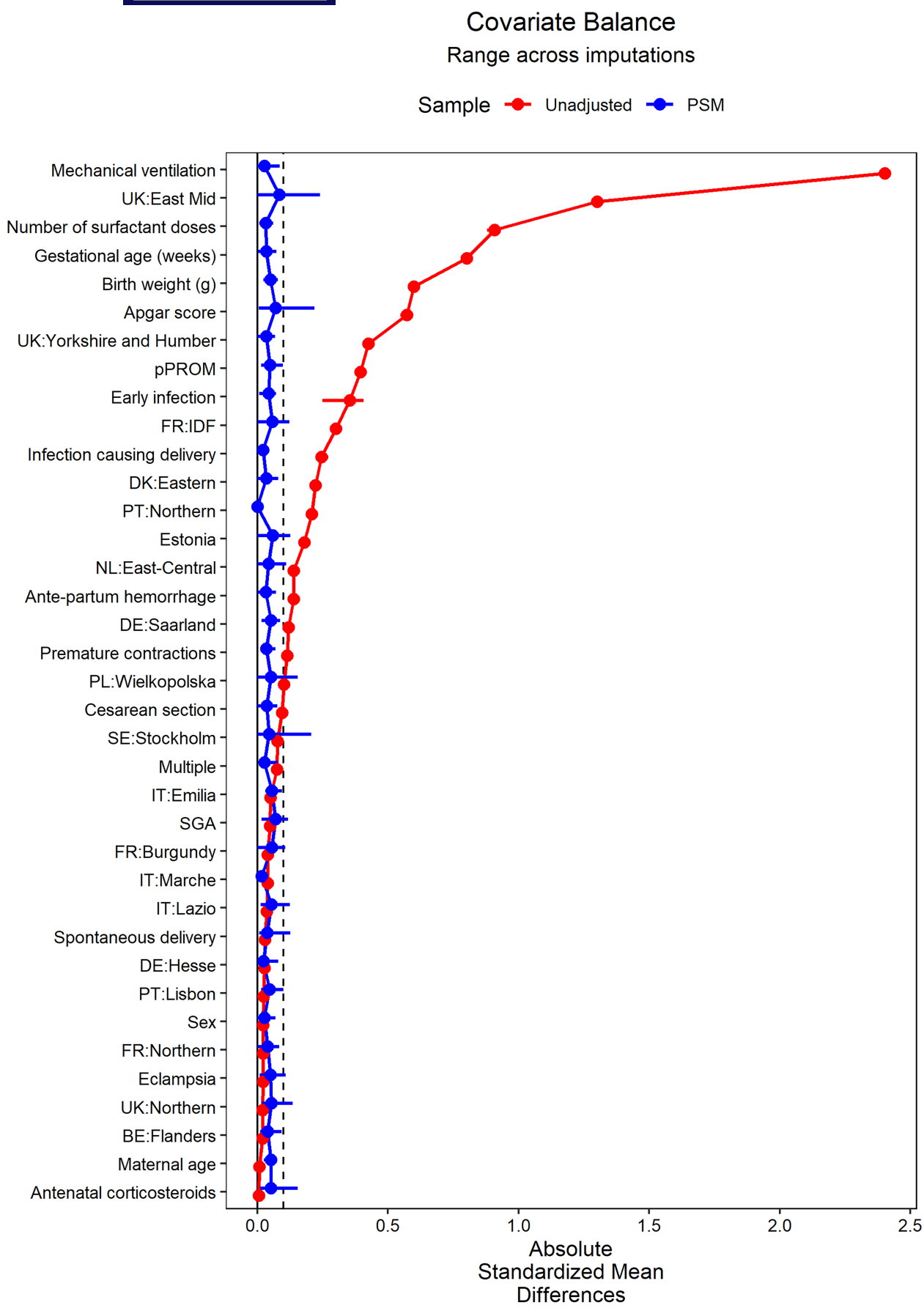

FIGURE 2 Goodness of propensity score matching. Differences between treated and untreated infants before • and after • matching, showing all the covariates. In the propensity score matched cohort the covariates were more balanced between the two groups, with all standardised mean differences (SMD) below the 0.20 threshold.

treatment. These were compared to the 3502/6316 (55.4%) of the infants who were not treated and alive and were followed up at 5 years of age. The children treated with iNO had a higher incidence of vision (45% vs. 20%), hearing (15% vs. 94%), motor (57% vs. 42%) and cognitive (30% vs. 25%) impairments than the non-treated controls in the total cohort. After matching, we found that patients treated with iNO had a slightly higher risk of cerebral palsy (OR 1.20, 95% CI 0.46–3.13), hearing impairment (OR 2.44, 95% CI 0.84–7.10), motor impairment (OR 1.3, 95% CI 0.73–2.31), speech delay (OR 2.00, 95% CI 0.78–5.12) and vision impairment (OR 1.81, 95% CI 0.89–3.71) than the controls. However, these differences were not statistically significant (Figure 5).

3.4 | Perinatal factors associated with iNO treatment and mortality

Explorative subgroup analyses revealed statistically significant interactions between treatment effects and gestational age ($p = 0.013$). Mortality was slightly increased in the treatment group, compared to the matching controls, when we examined the subgroup of patients born at <28 weeks (OR 1.68, 95% CI 1.01–2.79). In contrast, we found that iNO was associated with a significantly higher risk of mortality in patients who were born at ≥28 weeks (OR 4.29, 95% CI 1.72–10.72). Similarly, while iNO was associated with higher mortality in the absence of pPROM (OR 2.29, 95% CI 1.33–3.95), we did not observe any improved survival in the iNO group when it was present (OR 1.7 0.93–3.12). Deliveries prompted by infections did not affect the outcome, but delivery by Caesarean section did (Table S2).

4 | DISCUSSION

This study produced two major results. The first was that iNO was used for some VPT patients in all the participating countries but with variations across, and within, countries. Secondly, iNO was associated with increased in-hospital mortality, but it did not affect the neurodevelopmental outcome when patients reached 5 years of age.

Although iNO has been reported to promptly increase oxygenation in preterm infants,[19,20] it was not associated with decreased mortality. We actually observed the opposite. This could be because reducing pulmonary resistance promptly increases blood flow to the lungs and could reverse shunting through the ductus, leading to volume overflow in the lungs and pulmonary oedema. We also speculated that trying to increase oxygenation leads to oxidative stress, which has been associated with worse neurological outcomes.[21] Treating infants with iNO was associated with worse neurodevelopmental outcomes than the entire cohort. However, this difference was not significant when we corrected the data for important confounding variables.

In 2011–2012, when the iNO data for this study were collected, there were no European guidelines to support the use of iNO and it was discouraged in the USA.[22] Despite that, we found that iNO was used in all the European countries that participated in this study. However, there were considerable variations in the frequency (Figure 3). This finding was in line with several studies that suggested that neonatologists did not consistently follow evidence-based clinical practice recommendations.[23] The proportion of VPT infants treated with iNO was 4.0% in the current cohort, which reflects the same level of use during the same period in the USA.[24] There was a decline in iNO use in the USA in 2011, after the National Institutes of Health Consensus Development Conference[22] discouraged iNO treatment. However, this decline was very short-lived and its use increased again the following year.[24] In 2019, new recommendations emerged following a plenary session at the Paediatric Academic Society conference in Baltimore.[25] This stated that iNO could be used for preterm infants, if the current best evidence and experience showed that severe PPHN contributed to hypoxemia. New European guidelines were also published for managing respiratory distress syndrome in 2019, and renewed in 2023, but iNO was not included as a recommended treatment.[6]

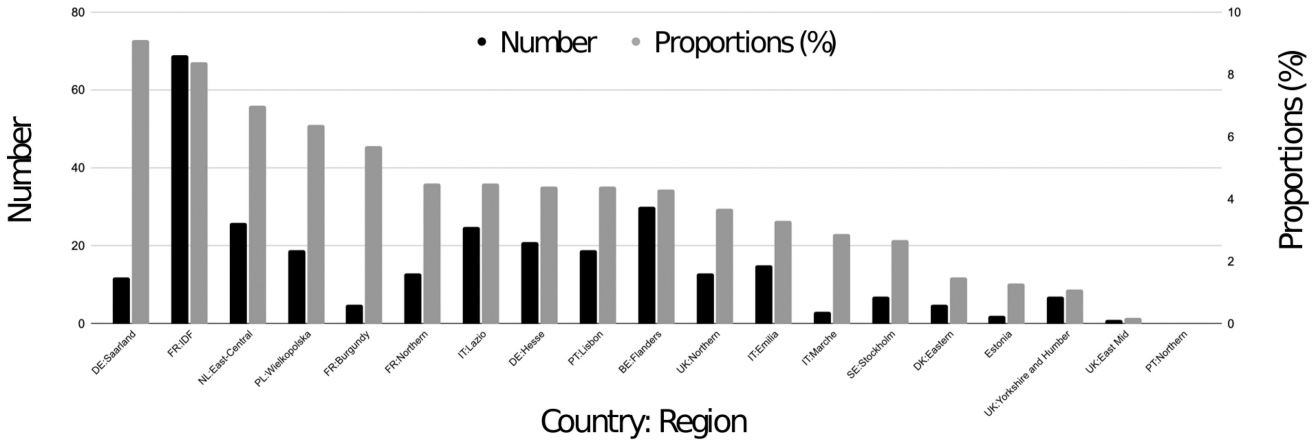

FIGURE 3 iNO use in the regions and countries. Total number • (*y*-axis to the left) and proportion • (*y*-axis to the right) of infants treated with iNO in each of the participating region in the EPICE/SHIPS cohorts The follow-up study comprised 292 subjects (4.0% of the total cohort). Country abbreviations: BE, Belgium; DE, Germany; DK, Denmark; FR, France; IT, Italy; NL, The Netherlands; PL, Poland; PT, Portugal; SE, Sweden; UK, United Kingdom.

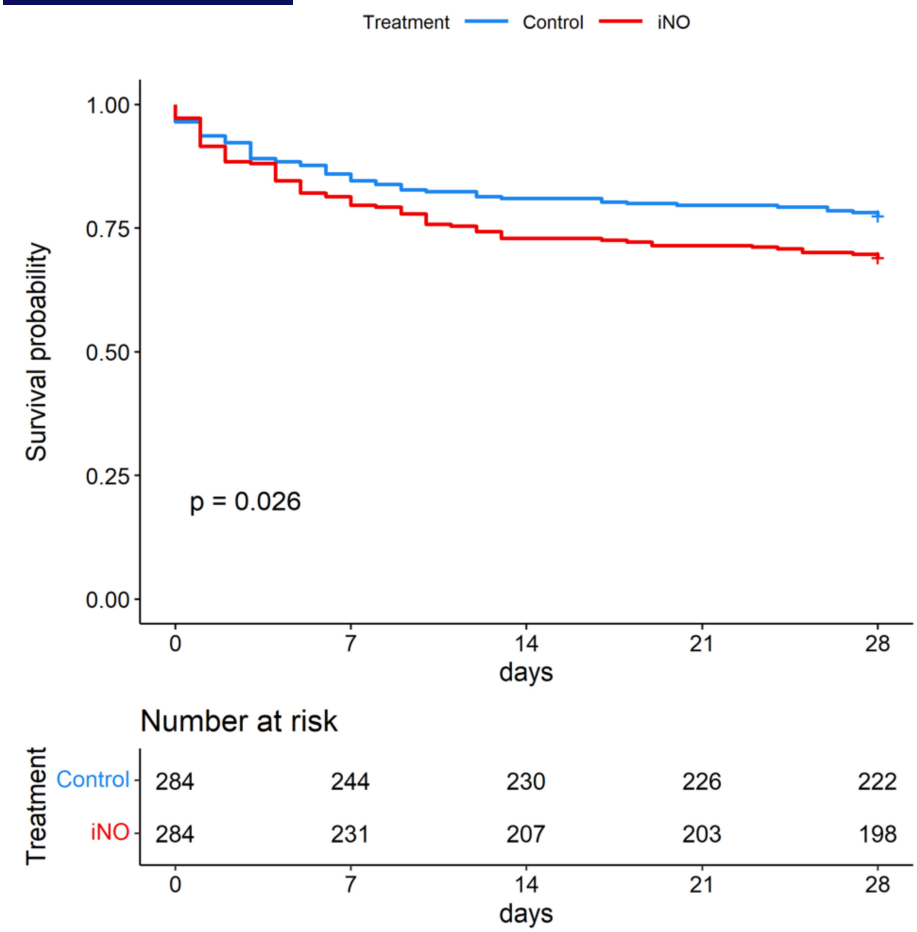

FIGURE 4 iNO and in-hospital survival. Kaplan–Meier curve depicting survival probability. Infants were born between 22 + 0 and 31 + 6 weeks of gestation in 2011–2012 in 19 regions across 11 European countries. The observation time was 28 days for all infants. The control group comprised 1:1 propensity scored-matched infants with equal pre-treatment morbidity. Infants treated with iNO had higher mortality, especially within the first 2 weeks of life ($p < 0.05$).

As well as recommending iNO for neonates with PPHN,[25] a number of studies have also suggested that it could be used for infants with respiratory distress syndrome following pPROM, oligohydramnios and lung hypoplasia.[26–28] The first two studies were both small, with eight exposed infants in each, and they had a short follow-up period that only evaluated short-term mortality and an oxygenation index.[26,27] The third study reported that iNO did not improve either the survival or morbidity of children with lung hypoplasia. Our study did not find that iNO was advantageous for pPROM, compared to not using it. In addition, we did not find that the duration of pPROM, as a proxy for lung hypoplasia,[29] affected the outcome. Our results also showed worse outcomes after iNO use for infants born at 28 weeks or more of gestation and for those delivered by Caesarean section. However, only a small number of patients fell into these categories and some of those results may have been the result of random chance.

4.1 | Strengths and limitations

The major strength of our study was that it was a large multicentre prospective study with a reasonable number of infants treated with iNO in 19 regions in 11 European countries. We had access to reliable and detailed perinatal data prior to iNO treatment and this made it possible to create a well-matched control group. In addition, this was, to the best of our knowledge, the first study to assess neurodevelopmental as late as 5 years of age. The loss of patients to follow up was high (44.4%), but in concordance with, or better than, previous studies.[14,16]

One of the limitations of this study was that it lacked information on both the PPHN diagnoses and information on whether echocardiography was performed before iNO was administered, as recommended.[25] This could reflect the true nature of clinical practice, where clinicians cannot wait for an echocardiography before using iNO in emergency or urgent situations. Moreover, evidence of PPHN, provided by echocardiography, has not been proven to affect the response to iNO in term and near-term infants.[30] This could be explained by the difficulties in distinguishing if the signs of PPHN were primarily of precapillary origin.[31]

Another major limitation was the lack of randomisation and blinding. Despite considerable efforts to eliminate bias through propensity score matching and other measures, it might be that the sickest infants were among those treated with iNO. Another major limitation of this study was the lack of information on the indications

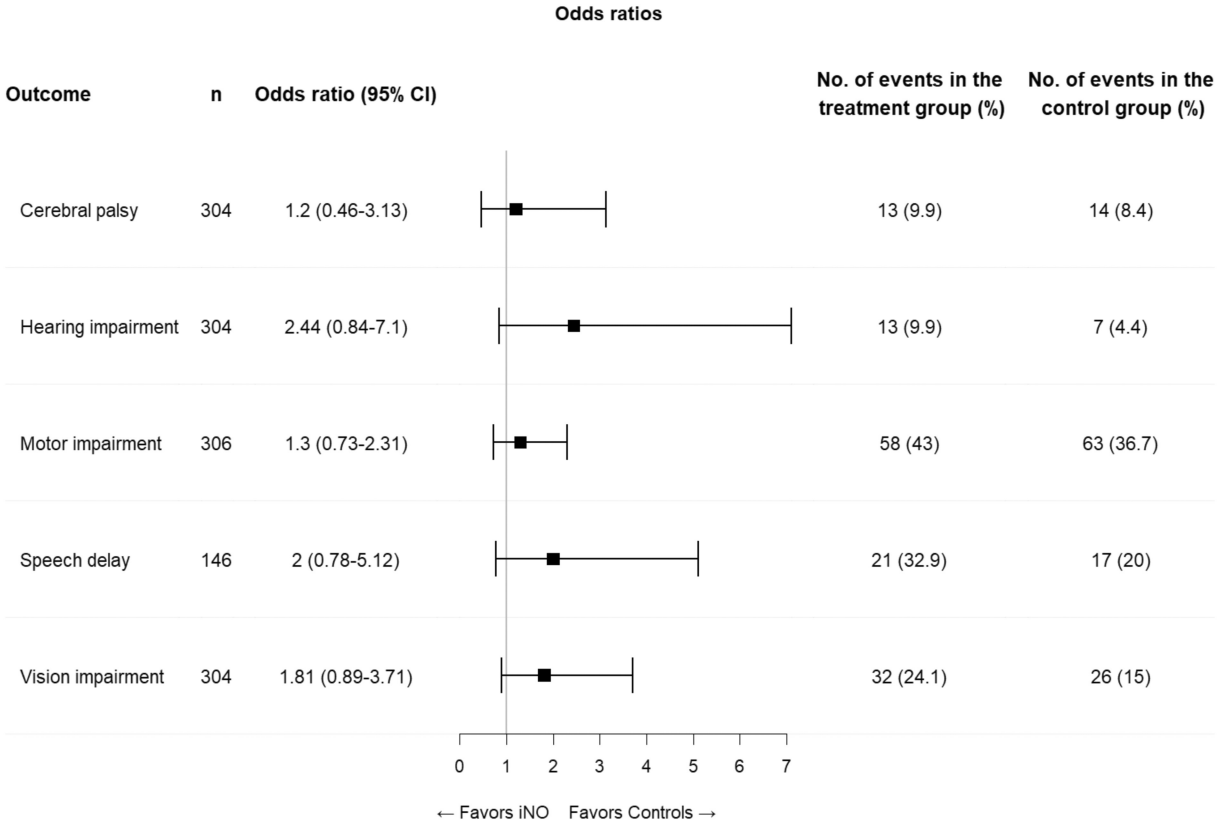

FIGURE 5 Neurodevelopmental impairment 5 years of age in children treated with iNO at birth. Differences in neurodevelopmental impairments (cerebral palsy, hearing impairment, motor impairment, speech delay and visual impairment) at 5 years. Data were gathered using a parental questionnaire, between iNO-treated infants and untreated propensity score-matched controls. Examined using logistic regression and presented as odds ratios and 95% confidence intervals.

for iNO treatment and the timing and duration. We assumed that iNO was used as a rescue treatment, which is the only recommended indication.[2,7] Moreover, they had no deaths in the European Union Nitric Oxide trial,[5] when iNO was used to prevent BPD. That is why we suggest that our finding of increased mortality in the first 2 weeks of life was likely to be due to infants receiving iNO as a rescue treatment.

5 | CONCLUSION

This study found an association between iNO use in VPT infants and increased in-hospital mortality, but neurodevelopmental outcomes at 5 years of age were not affected. The ethics of using iNO in routine clinical practice is dubious. We could argue that all clinicians have an ethical responsibility to use all the treatments that they feel may save lives. However, they also have an ethical responsibility to withhold such treatment when evidence of efficacy is missing. An acute clinical response to iNO does not have to be equivalent to the benefits of survival. Moreover, the cost of using iNO without evidence of effectiveness cannot be ignored.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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