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Title	A population-based comparison of preterm neonatal deaths (22–34 gestational weeks) in France and Ontario: a cohort study
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Reviewer 1	Bengt Källén
Institution	Lund University, Tornblad Institute, Lund, Sweden
General comments (author response in bold)	This manuscript compares neonatal survival in infants born before week 35 in two populations Difference in survival was noted for weeks 22-26, a smaller difference for weeks 27-31, and none for week 32-34 with a higher death rate in the French than in The Canadian data. After further adjustment for mode of delivery, antenatal steroid use and delivery in a hospital with a level 3 neonatal unit, the difference between the populations if anything increased, at least for infants born at <32 weeks. The report is well presented and the conclusions are drawn with care. I have only few comments to make: 1. Many readers would have liked an adjustment for actual delivery week in the analyses made for groups of delivery weeks. I don´t believe, however, that it would change the conclusions (to judge from Figure 1 where a difference is seen for each individual week). **We thank the reviewer for this comment and would like to re-iterate that the gestational week groups were chosen to be consistent with previous EPIPAGE2 publications. As the reviewer pointed out, the gestational age specific proportions are presented in figure 1. To better represent this, we have modified the existing sentence: "Gestational age was categorized into 3 discrete groups: 1) 22-26 weeks, 2) 27-31 weeks and 3) 32-34 weeks for ease of comparison of BORN Ontario to the EPIPAGE-2 cohort."** **[Page 4, Methods]** **to the following:** **"To be consistent with previous EPIPAGE2 publications, we categorized gestational age into 3 discrete groups: 1) 22-26 weeks, 2) 27-31 weeks and 3) 32-34 weeks."** **[Page 4, Methods]** 2. Gestational week is a critical item but I cannot find information as to what extent gestational age was based on sonographic determinations in the two populations. **Excellent point. Both EPIPAGE 2 and BORN estimated gestational age using a combination of dating ultrasound and the date of the last menstrual period. This detail has been added to the manuscript with the following sentence in the methods section:** **"Both cohorts used a combination of dating ultrasounds and the date of the last menstrual period to estimate gestational age."** **[Page 4, Methods]** 3. I wonder if a sub-analysis with exclusion of infants born after ART and one after exclusion of multiple births would change the results, notably for the 22-26 week group. On p.7, line 24 it is mentioned that ART gives an increased multifetal rate - but also an increased rate of preterm and very preterm births. **Thank you for pointing this out. However, ART and multifetal gestations are explanatory variables used in the adjusted models presented in table 4 (comparing neonatal death). The effect of these two variables is already accounted for within our analyses.**
Reviewer 2	Tetsuya Isayama
Institution	Neonatal Intensive Care Unit, Sunnybrook Health Science Centre, Toronto, Ont.
General comments (author response in bold)	This is a cohort study comparing the maternal and obstetrical characteristics and mortality of preterm infants between the two population-based cohorts in France and Ontario, Canada. It found that there was a great difference in infants' mortality, in particular in those at extremely low gestational ages (e.g. 22-26 weeks). Although the study found variations in the maternal and obstetrical characteristics between the two cohorts, these differences did not explain the difference in infants' mortality. Although the topic was interesting and important, the interpretation of the results was limited due to the lack of the data on neonatal morbidities as well as ethical decision making for extremely preterm infants. I put several major and minor comments below. Major comments 1. In the Table 1 and 2, there was an extreme difference in the proportion of still births between the two cohorts especially at very low gestational age. The EPIPAGE cohort had extremely high still births rate than Ontario one at 22-23 weeks gestations (84.6% vs. 47.6% at 22 weeks, 76.0% vs. 29.7% at 23 weeks). What is the reason? Are the definition (or registration practice) of still births and live births different between the two cohorts? Does it indicate that some live births at 22-23 weeks gestations in France were registered as still births because these infants were considered not-viable? If so, the denominators (live births) of this study have big problems. Or, is the differences due to the different population coverage of still births between the two cohorts? Or, is it due to the difference in obstetric care for these periviable gestations? Can the author explain the potential reasons? **We thank the reviewer for allowing us an opportunity to explain. The definition of stillbirths in the two cohorts is the same. BORN Ontario's capture of still births is not consistent and exhaustive so the difference could be related to under-reporting rather than a realized difference. We have added this to the manuscript with the following sentence:** **"There is also a higher rate of stillbirths in the French cohort, and while this could be related to less aggressive obstetrical management, it is difficult to speculate on the exact reason as the BORN data on stillbirths may not have full capture. This will need to be explored further in future studies."** **[Page 10, Interpretation]** 2. Page 3, Lines 8-9: Could the author explain the reason for why they categorized the gestational age into 22-26, 27-31, and 32-34 weeks. Previous papers reported that in France infants < 24 wk GA receive only palliative care (Arch Pediatr. 2010 May;17(5):527-39) while in Canada the decision is individualized for each infant and family for infants 23-25 wk GA (Paediatr Child Health 2012;17(8): 443). This explains the almost 100% mortality of those at 22-23 weeks gestations in France. Therefore, it is probably more reasonable to assess the infants at 22-23 weeks separately from those at > 23 weeks in the comparison between the two cohorts. **Thank you for allowing us the opportunity to explain. The categories were chosen to be in line with previous publications from the EPIPAGE 2 cohort. At the time of the Ontario cohort (2012-2013) the recommendation from the CPS position statement was to not resuscitate babies born at 22 weeks (similar to France) and a shared decision making model was to be used at 23-25 weeks. In France the zone of shared decision-making is between**

24-25 weeks. Therefore the only group where approach to antenatal counseling would have been different is the 23-week group. The individual gestational age groups are compared separately in Figure 1 thus there would be no change in our conclusions by separating out the 23-week gestation age group for our analysis since the difference in mortality extends well beyond the "grey zone" for decision making regarding resuscitation. We have explained this further in our discussion by adding in the line:
"At the time of the cohorts, the general consensus in France was to not offer resuscitation at <24 weeks although no specific guidelines exists. In the Ontario cohort, the Canadian Pediatric Society guideline recommended no resuscitation at <23 weeks with a parental discussion between 23-25 weeks (20,21). This may explain some of the differences in survival at the limits of viability. Nonetheless this would not explain the difference in mortality of babies born >24 weeks."
[Page 9, Interpretation]

We also performed additional analysis by excluding babies born <24 weeks. The general trend even with these babies excluded is for a higher proportion of neonatal death per live birth in France, however, with the reduction in sample size, it was not statistically significant. We included this in our results.
"We performed further analysis by excluding the babies born at <24 weeks gestation. After adjustment for all the same factors the aOR for neonatal death was 2.76 (95% CI: 0.98, 7.76). While this suggests a trend towards higher mortality in France even with 22-23 week GA babies excluded, it was not statistically significant due to the loss of power from the reduction in sample size."
[Page 7, Results]

3. Page 4, Lines 10-15 and Table 4: The authors assessed deaths within 1 month and that within 5 months and did not find major difference in the results between the two (1 month and 5 month). It is no surprise because most of the deaths occurred within 1month of age as the author mentioned in the manuscript. It would be interesting if the authors could assess the deaths after > 1 hour of birth (or after > 1 day of birth) because the ethical decision of non-resuscitating infants or the registration practice of still births and very severe live births mainly affect the deaths shortly after births (e.g. < 1 hour, or < 1 day). The comparison of deaths excluding deaths that happened shortly after births can provide important information regarding whether the difference in mortality between the two cohorts was due to these factors or others.
Unfortunately, the information needed to assess the time of death within the same day was not available in either cohort and we are unable to answer the reviewer's question. We added the following line to our limitations to address this:
"We were also unable to compare the exact day-time and cause of death which may have provided further insight towards approaches to decision-making"
[Page 10, Interpretation]

4. Page 8, Line 19 - Page 9, Line 26: The author mentioned the ethical attitude for resuscitating extremely preterm infants as well as withdrawal and withholding of treatment for them might explain the difference in infants' mortality. I agree with this authors' opinion. However, the difference in clinical practice may be another potential reason for the mortality difference. In this sense, the lack of the data on morbidities (IVH, NEC, BPD, sepsis, etc.) as well as neonatal management practice is a major limitation of this study. At least, could the author discuss or speculate how the management of extremely preterm infants as well as their morbidities are different or the same between the two cohorts except for the ethical decision making (e.g. circulatory management, respiratory management)?
We agree this is a limitation of the study and we have noted this in our discussion, with the following sentence:
"In addition, while we speculate that the difference in mortality may be related to variations in ethical decision-making, there could also be significant differences in the post-natal management of these preterm infants which will need to be explored further."
[Page 11, Interpretation]

Minor comments
1. Page 2, Lines 17-18: the referernces (9, 10) did not explain the detail of the databases.
We have added the BORN website as a database, hopefully this will provide the additional details needed.

2. Page 2, Lines 19-20: Very preterm infants is generally around < 33 wk GA. Better to use the word preterm infants of <- 34 wkGA) (in WHO definition, very preterm < 33 wk GA)
We thank the reviewer for this comment, which will ensure our terminology is consistent with the WHO definition. We have subsequently changed the wording throughout the manuscript.

3. Page 2, Line 42 - Page 3, Line 4; Table 3: Are the definitions of the maternal or obstetrical variables the same between the two databases? Do the antenatal steroids include one dose of antenatal steroid (incomplete antenatal course)? What is the definition of level 3 NICU?
Yes the definitions of the variables are the same, we cross referenced the variable definitions to make sure they match. We have added the following sentence to the methods section to note this.
"All variable definitions were compared to ensure matching between the two cohorts. Co-variates were chosen based on clinical relevance..."
[Page 4, Methods]

4. Page 3, Lines 14-24: Although the cohorts were considered population-based, if possible, it would be better to mention about the population coverage (100%?) or the proportion of lost-to-follow-up of study infants?
BORN captures 100% of hospital births in Ontario and there should be no loss to follow-up for the outcome, and EPIPAGE 2 is a population-based cohort representative of 25 of 26 regions in France and there is no loss to follow-up either for the intents of this study. Participation rates in EPIPAGE 2 during the period of recruitment were 92.6% in infants born 22-26 weeks, 93.6% among those born 27-31 weeks and 89.7% at 32-34 weeks.

5. Page 3, Lines 45-50: The author did not mention the maximum time period for neonatal deaths. How long did they follow the neonates to check whether they died or survived? Please clarify it.
The follow up period for neonatal deaths was 1 year for both Ontario and France.

6. Page 9, Lines 10-15: It was not clear what the author meant by the sentence that "It is possible the difference in attitudes towards the outcomes of these preterm infants occurs after post-delivery assessment." Could the author clarify it?
Thank you for pointing out this typo, we have revised this sentence to read:

	"It is possible that there is also a difference in the approach of clinicians towards these infants based on post-delivery assessment of the infant's clinical status with a lower threshold for transitioning to palliative care in France." 7. Discussion: Because there are the clinical guidelines or policy statements regarding the decision making on management of extremely preterm infants (22-25 weeks gestations) in both France and Canada (Arch Pediatr. 2010 May;17(5):527-39; Paediatr Child Health 2012;17(8):443), the author should mention about theses guidelines in the discussion. **We have included these articles in the discussion.** **[Page 9, Interpretation]**
Reviewer 3	Thuy Mai Luu
Institution	Département de pédiatrie, CHU Sainte-Justine, Montréal, Que.
General comments (author response in bold)	It has always been suspected that short-term outcomes of preterm babies born in France might differed from that of Canadian newborns due to differences in philosophy of care (and life), French neonatologists being less aggressive and more prone to withdraw treatment for infants suffering multiple complications. This retrospective analysis of two prospective cohorts in the province of Ontario (BORN cohort) and France (EPIPAGE-2) confirms that mortality is indeed higher in France versus Canada for infants born at 22-26 weeks ($p<0.0001$), even after adjusting for intrinsic factors and perinatal practices that should have favored French babies The novelty is questionable as it is already known that there is variation between developed countries in survival and morbidities. Wang et al's analysis is however more refined as they had access to a more complete dataset. How is it going to change our practices? This is the main issue with this study which can only tell that French babies born at 22-26 weeks' gestational age are more likely to die in the first month of life. Even if authors postulated on different perceived survivability, it would have been interesting to compare initial physiological scores (e.g. SNAP) or neonatal complications (e.g. early head ultrasound findings). In addition, knowing whether better survival was observed at the cost of worse long-term neurodevelopmental outcomes would have been informative. Authors do recognize these limitations. Most likely that data to answer these questions were not available in the BORN database. **Yes, we agree that there are shortcomings in the data and that this prevents us from conducting the suggested analyses. We highlight these shortcomings in the limitations.** **However, we strongly believe this study is novel as it is the first time we can adjust on antepartum and peri-partum factors that are known to effect neonatal mortality. We demonstrate that despite adjustment for these factors there is still significant differences in mortality between the two cohorts. This shows the potential impact a difference in attitude may have on the survival of preterm babies.** **Although we did not have data on long term neurodevelopmental outcomes, we have included in our discussion a comparison of the 2017 manuscript from the Canadian neonatal follow-up network as well as the EPPIPAGE 2 long term follow up manuscript which would not suggest there is worse long-term neurodevelopmental outcomes in the Ontario cohort.**