BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024560
Article Type:	Research
Date Submitted by the Author:	01-Jun-2018
Complete List of Authors:	Adams, Mark; Universitätsspital Zürich, Department of Neonatology; University Zurich, Epidemiology, Biostatistics and Prevention Institute Berger, Thomas; Kinderspital Luzern, Neonatal and Paediatric Intensive Care Unit Borradori-Tolsa, Cristina; Geneva University Hospital, Department of Paediatrics, Bickle-Graz, Myriam; University Hospital Lausanne, Department Woman-Mother-Child Grunt, Sebastian; Children's University Hospital, Inselspital, University of Bern, Division of Neuropaediatrics, Development and Rehabilitation Gerull, Roland; University of Basel Children's Hospital (UKBB), Department of Neonatology Bassler, Dirk; University Hospital Zurich, Department of Neonatology Natalucci, Giancarlo; UniversitatsSpital Zurich,
Keywords:	NEONATOLOGY, Fetal medicine < OBSTETRICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Perinatal interventional activity affects 2-year outcome of Swiss extremely preterm born infants

Mark Adams MSc[1,2,3], Professor Thomas M. Berger MD[2], Cristina Borradori-Tolsa MD[4], Myriam Bickle-Graz MD[5], Sebastian Grunt MD[6], Roland Gerull MD[7], Professor Dirk Bassler MD, MSc[1], and Giancarlo Natalucci MD[1,2,8] for the Swiss Neonatal Network & Follow-Up Group

AFFILIATIONS
[1]Department of Neonatology, University of Zurich and Zurich University Hospital, Zurich, Switzerland;
[2]Swiss Neonatal Network & Follow-up Group, Zurich, Switzerland;
[3]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland;
[4]Department of Paediatrics, Geneva University Hospital, Geneva, Switzerland;
[5]Clinic of Neonatology, Department Woman-Mother-Child, University Hospital Lausanne, Lausanne, Switzerland;
[6]Division of Neuropaediatrics, Development and Rehabilitation, Children's University Hospital, Inselspital, University of Bern, Bern, Switzerland;
[7]Department of Neonatology, University of Basel Children's Hospital (UKBB), Basel, Switzerland;
[8]Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland.

CORRESPONDING AUTHOR
Mark Adams, Department of Neonatology, University Hospital Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland; Tel. +4144 556 3034; mark.adams@usz.ch.

Short title

Perinatal intervention activity affects 2-year outcome

Financial Disclosure Statement

Mark Adams receives a salary as network coordinator for the Swiss Neonatal Network. Giancarlo Natalucci received financial support by the Swiss National Science Foundation; grant PZOOP3_161146. The remaining authors have indicated they have no financial relationships relevant to this article to disclose.

Funding

The authors received no specific funding for this work. The sponsors were not involved in the following matters: study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the manuscript for publication.

Conflict of Interest Statement

Potential Conflicts of Interest: Mark Adams receives a salary as network coordinator for the Swiss Neonatal Network. The remaining authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

List of abbreviations

aOR: adjusted odds ratio; AUC: area under receiver operator characteristic (ROC) curve; BSIDII: Bayley Scales of Infant Development, second edition; Bayley-III: Bayley Scales of Infant and Toddler Development, Third edition; BPD: bronchopulmonary dysplasia; CI: confidence interval; cPVL: cystic periventricular leukomalacia; GA: gestational age; GMDS: Griffith scales of Infant Development; GMFCS: Gross Motor Function Classification System; IVH: intraventricular haemorrhage; LOS: late onset sepsis; NDI: neurodevelopment impairment; NEC: necrotizing enterocolitis; NICHD NRN: national institute of child health neonatal research network; ROP: retinopathy of prematurity; SD: standard deviation; SES: socio-economic status; SNN: Swiss Neonatal Network & Follow-up Group.

ABSTRACT

Objectives: To investigate if centre-specific levels of perinatal interventional activity were associated with neonatal and neurodevelopmental outcome at two years of age in two separately analysed cohorts of infants: cohort A born at 22 to 25, and cohort B born at 26 to 27 gestational weeks, respectively.

Design: Geographically defined, retrospective cohort study.

Setting: All nine level III perinatal centres (neonatal intensive care units (NICUs) and affiliated obstetrical services) in Switzerland.

Patients: All live-born infants in Switzerland in 2006-2013 below 28 gestational weeks, excluding infants with major congenital malformation.

Outcome measures: Outcomes at 2 years corrected for prematurity were mortality, survival with any major neonatal morbidity, and with severe-to-moderate neurodevelopmental impairment (NDI).

Results: Cohort A associated birth in a centre with high perinatal activity with low mortality (aOR: 0.22; 95% confidence interval: 0.16-0.32), while no association was observed with survival with major morbidity (aOR: 0.74; 95% confidence interval: 0.46-1.19), and with NDI (aOR: 0.97; 95% confidence interval: 0.46-2.02). Median age at death (8 versus 4 days) and length of stay (100 versus 73 days) were higher in high than in low activity centres. The results for cohort B mirrored those for cohort A.

Conclusions: Centres with high perinatal activity in Switzerland have a significantly lower risk for mortality while having comparable outcomes among survivors. This confirms results of other studies but in a geographically defined area applying a more restrictive approach to initiation of perinatal intensive care than previous studies. The study adds that infants up to 28 weeks benefited from a higher perinatal activity and why further research is required to better estimate the added burden on children who ultimately do not survive.

Strengths and limitations of this study

- Geographically defined cohort study comparing 2-year outcome of extremely preterm infants between hospitals with high and low perinatal interventional activity based on a quantitative score of 3 obstetric and 4 neonatal indicators.
- Crude and risk-adjusted odds ratios for outcome between high and low activity centres were calculated using regression models and measuring predictive validity of risk adjustment.
- Missing outcome data of surviving infants lost to follow-up were addressed by multiple imputation and the validity of data imputation was tested by sensitivity analysis using non-imputed data.
- Further minor limitations are represented by the composite nature of the definitions of the perinatal interventional activity and of the neurodevelopmental outcomes, which could have led to a loss of information.

Keywords
Extremely preterm, limit of viability, perinatal intervention, mortality, morbidity, 2 year outcome

Word count
3239

INTRODUCTION

Over recent decades, progress in perinatal care has led to vastly improved survival rates for infants born at extremely low gestational age (GA). Consequently, the GA limit for initiating life-sustaining intensive care at birth was lowered to 22 weeks, below which treatment is generally not recommended.[1] This however raised ethical concerns regarding the added burden to infants who ultimately do not survive and the increased risk of neurosensory impairment among those that do survive.[2] There is little consensus about the policy of treating these infants. Instead, hospital practices regarding the initiation of intensive care have dramatically influenced rates of survival and survival without impairment.[3] This has led to large outcome variation among hospitals. In 2015, Rysavy et al. quantified the effect of perinatal interventional activity on outcome between a group of 24 centres of the NICHD NR network in the United States. Among infants born at 22-23 weeks gestation, centre rates of active treatment accounted for 78% of the variation in survival between centres. For those born at 24 weeks gestation it accounted for 22% of the variation.[4] There is a similar variation in decision making approaches in Europe, which appears to reflect local philosophy and practice rather than economic or demographic markers, individual variations in health expenditure or rates of preterm birth.[5] Swiss obstetricians and neonatologists are known to be generally restrictive with regards to initiation of intensive care for infants at the limit of viability. A recent study revealed that the decision-making regarding initiation of treatment was based almost exclusively on gestational age (GA) and that most infants born < 24 weeks gestation received a priori comfort care.[6] Nevertheless, centre-to-centre outcome variability has repeatedly been reported and is assumed to be in part associated with the local ethical decision making.[7–9] What remained unclear was whether the lower mortality in some centres lead to higher risk of neurodevelopmental impairment (NDI) in survivors.

This study aimed to quantify the outcome differences between centres with a higher propensity towards providing active perinatal care at birth from those that provide more a priori comfort

care. We assessed infants in cohort A (22+0 to 25+6 weeks gestational age (GA)) and compared their outcome variability with that in cohort B (26+0 to 27+6 weeks GA) where we expected no difference in either perinatal care provision or outcome based on previous studies.[4,10–13]

METHODS

Study population and procedure

Geographically defined, retrospective cohort study including all live born infants between 22+0 to 27+6 weeks of gestation in Switzerland from 2006-2013. We excluded infants born with a major congenital malformation, defined as being the primary cause of death or requiring surgery or a chromosomal anomaly. We also excluded 4 infants born and treated exclusively in 3 stepdown units. We extracted electronically recorded data (challenged for plausibility and completeness) from the prospective national database of the Swiss Neonatal Network & Follow-up Group (SNN). Data from delivery room deaths were audited by a researcher visiting the hospitals' maternity wards.

Data collection and evaluation for this study has been approved by the institutional ethical review board (KEK-ZH-Nr 2014-0552). Participating centres were obliged to inform parents about the scientific use of anonymized data.

Neonatal data

Perinatal and neonatal variables were defined as follows: GA as the best estimate available based on prenatal ultrasound examination during the first trimester of pregnancy. Birth weight z-scores, intraventricular haemorrhage grade 3 or higher (IVH), cystic periventricular leukomalacia (cPVL), bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity stages 3-4 (ROP), necrotizing enterocolitis (NEC), late onset neonatal sepsis (LOS), and Socioeconomic status (SES) were defined as previously published.[14]

Neurodevelopmental outcome at 2 years of age

Experienced neuro- or developmental paediatricians performed the standardized Swiss follow-up assessment[15] at 18-24 months corrected age in one of the Swiss follow-up centres. Between 2006 and 2012, examinations were based on Bayley Scales of Infant Development, 2. edition (BSID-II)[16] and afterwards on Bayley scales of infant and toddler development, 3. edition (Bayley-III).[17] According to recent literature,[18–20] Up until 2006, some of the children were tested using the Griffiths mental development scales-Revised (GMDS)[21] during the transition period to BSID-II. Bayley-III scores below 85 (-1SD) were considered as equivalent of indices below 70 (-2SD) in the BSID-II and the GMDS. Infants with significant disability precluding completion of the development test were assigned a development score of 1 below -3SD. Cerebral palsy was defined according to Rosenbaum[22] and was graded according to the Gross Motor Function Classification System (GMFCS) For Children Aged ≤ 2 Years.[23] Vision and hearing were assessed by either direct examination or caregiver report.

Perinatal interventional activity score

In order to differentiate between Swiss centres with a higher propensity to initiate intensive care for infants born below 26 weeks gestation we calculated a perinatal activity score per centre based on the model presented by Serenius et al. in 2015.[10] Obstetric and neonatal activity scores reflecting the intensity of care in each centre were calculated on the basis of the rates of 3 key obstetric indicators (delivery at level III hospitals, i.e. inborn; complete course of antenatal steroids; caesarean section), and 4 key neonatal indicators (surfactant within 2 hours after birth; any of the following activities in the delivery room: bag/mask ventilation, continuous positive airway pressure, endotracheal intubation, epinephrine or adrenaline supply, cardiac compression; no recorded decision for primary non-intervention in the delivery room [available for all infants]; infants admitted for intensive care [out of infants alive at 30 minutes after birth]). The mean

obstetric and neonatal activity scores comprised the perinatal activity score (henceforth, activity score). Each step included normalization by assigning the centre with the highest rate for each indicator a score of 100; the remaining centres were assigned proportional scores. We calculated an activity score for infants born between 22-25 weeks gestation (cohort A) and a separate one for infants born 26-27 weeks gestation (cohort B). The first score was used to classify the nine Swiss perinatal centres into a "low" and a "high" activity group using the arbitrary threshold of an activity score of 80. To allow comparison between cohort A and cohort B, cohort B was split into the same centres with low and high activity as for cohort A. To confirm the dichotomous association of perinatal activity with outcome, we also tested for a linear association. For this, we generated a variable that increases by one for every 5-point increase in perinatal activity using the two perinatal activity scores for cohort A and B.

Outcome

Outcome parameters were defined as follows: mortality at 2 years corrected age, death or moderate-to-severe NDI, death or major morbidity, survival with moderate-to-severe NDI, and survival with major morbidity. Moderate-to-severe NDI was defined as either mental or motor development index below 70 (-2SD) in the BSID-II; cognitive or motor composite score below 85 (see below) in the Bayley-III; a global score of the GMDS below 70 (-2SD); cerebral palsy with GMFCS above 1; the absence of useful hearing even with aids (i.e. >90dB hearing level); blindness or only perception of light. Major morbidities encompassed IVH, cPVL, BPD, ROP, NEC or LOS.

Data completeness

Patient population coverage was assessed by comparison with the birth registry of the Swiss Federal Statistical Office and yielded 86.4% of all live births between 22-27 weeks gestation. Data per item was missing in 1.2% of datasets for the outcome "major morbidity" or less than

0.1% in all other cases. As 2-year follow-up data was missing in 11% of all surviving infants between 22-25 weeks gestation and 17% between of 26-27 weeks gestation, we performed a fivefold imputation with chained equations for the cohorts A (all infants), A (survivors), B (all infants) and B (survivors), respectively, allowing the calculation of pooled adjusted odds ratios (aOR) for the above listed outcomes.[24] Data for imputation were determined as missing at random. As a sensitivity analysis, we performed the same tests with crude, i.e. non-imputed data,

Statistical analysis

We performed multivariable adjusted logistic regression to compare outcome between centres with lower and higher perinatal activity. Adjustment was made for GA, GA^2 (to better model the non-linear dependency of most neonatal outcomes on GA), birth weight z-score, male sex, multiple births, outborn, and socio-economic status. To estimate the validity of the adjustment, we calculated how well the variables listed above predicted outcome. If this predicted validity is low, the adjustment made has limited explanatory power.[25] We calculated the area under receiver operating characteristics curve (AUC). AUC values between 0.7-0.8 were considered to represent moderate, and >0.8 to represent high predictive validity, respectively. All statistical analyses were performed using R Version 3.4.[26]

RESULTS

Study population and neonatal data

A total of 2063 infants were born alive in Switzerland between 2006 and 2013 (Figure 1). 1839 of those infants were registered by SNN between 2007 to 2013. They correspond to 1900 life-births registered at the Swiss Federal Statistical Office in the same time period which results in a population coverage of 97% for the study period (reference data for 2006 were not available as GA was not included in the national register prior to 2007). Of the 2063 infants we excluded 4 infants because they were born in and treated at 3 stepdown units and 85 infants because of major congenital

malformations. Among the 1974 included infants, 712 (36%) died before discharge and 6 (0.3%) after discharge but before reaching two years of age. In cohorts A and B, 319 (89% of survivors) and 743 (83%) were assessed at 2 years corrected age, respectively. 194 (15%) children were lost to follow-up (109 refused follow-up, 57 could not be reached/moved away, 28 unknown loss to follow-up). In both cohorts, difference between baseline characteristics of children with and without follow-up was negligible (Table 1), particularly concerning the factor "activity score" which determines the comparison groups for the subsequent analysis. Outborn children were less frequently assessed in both cohorts.

Perinatal interventional activity score

Table 2 displays the proportion of infants receiving either of the treatments determining the obstetrical activity (items [1] – [3]) and the neonatal activity (items [4] – [7]) for cohort A in each centre. Activity scores were determined out of the mean of the obstetric and neonatal activity scores and ranged from 57 to 98. Four centres with an activity score < 80 were classified as "low activity centres" with the remaining five centres classified as "high activity centres". A separate centre specific activity score was determined for cohort B using the same routine (supplemental Table 1). Each 5-point increase in perinatal activity score reduced the risk for mortality within two years of life for cohort A (aOR: 0.74, 95% confidence interval [CI] 0.68-0.81) and cohort B (aOR: 0.82, 95% CI 0.69 to 0.96).

After risk adjustment, the aOR in cohort A for mortality (0.22, 95% CI 0.16-0.32) and death or NDI (0.31, 95% CI 0.21-0.44) were significantly lower (Figure 2) for high compared to low activity centres. After restricting the cohort to survivors, aOR for any major neonatal morbidities was 0.74 (95% CI 0.46-1.19) and for moderate to severe NDI 0.97 (95% CI 0.46-2.02). The crude baseline characteristics of low versus high activity centres in cohort A (Table 3) were comparable for size, GA range, birth weight z-score, multiple births and SES. However, High

activity centres had more male infants and less outborn infants. The crude outcome proportions reflect the aOR results. Repeating the same evaluation using non-imputed data resulted in almost the same point-estimates and confidence intervals (dotted lines in Figure 2). Excluding the delivery room deaths, median NICU age at death in high activity centres was higher (8 versus 4 days) as was length of stay (100 versus 73 days). As can be seen in Figure 3, the distribution of age at death was different between high and low activity centres. In high activity centres, the highest density was reached above the median, whereas it was below the median in low activity centres. The violin plot thereby allows taking the full distribution of the data into account rather than relying on median and interquartile range alone.

Centres classified as having "high activity" for cohort A, still had a higher perinatal activity score (91 vs. 84) in cohort B with matching outcome variability. aOR for mortality (0.49, 95% CI 0.34-0.71) and death or NDI (0.72, 95% CI 0.53-0.97) were significantly lower in high activity centres (Figure 2). In contrast to cohort A the aOR for any major morbidities was also significantly lower (0.63, 95% CI 0.48-0.84) whereas moderate to severe NDI outcome in survivors was higher without reaching significance (1.17, 95% CI 0.77-1.78). Again, crude baseline characteristics (Table 3) were comparable with more male and fewer outborn infants in high activity centres. Crude outcomes mirror the aOR result. In cohort B, median age at death in NICU in high activity centres was again higher (11 versus 6 days), whereas length of stay was only somewhat longer (85 versus 78 days).

Neurodevelopmental outcome at 2 years of age

Follow-up assessment was performed at a mean (SD) corrected age of 22.6 (3.1) months (Table 4). Of 1062 examined children, 729 (69%), 265 (25%), and 46 (4%) were assessed with the Bayley-II, Bayley-III, and GMDS, respectively while in 19 (2%) children only a part of a developmental assessment could be performed because of severe cerebral palsy or poor

compliance. 220 (21%) infants suffered from moderate-to-severe NDI and 842 (79%) infants showed favourable outcome.

DISCUSSION

Swiss perinatal centres with a higher score of perinatal activity for infants at the borderline of viability (cohort A) had significantly lower aOR for mortality and for the composite outcome death or NDI. After restricting the cohort to survivors at two years of age corrected for prematurity, there was no significant difference between centres with high and low intensity regarding risk for major morbidity or NDI. Cohort B mirrored the outcome differences between high and low activity perinatal centres determined for cohort A, i.e. significantly lower aOR for mortality and for death or NDI. In contrast to cohort A, the lower mortality in high activity centres in cohort B was based exclusively on NICU mortality. High activity centres in cohort B had a significantly lower aOR for any major neonatal morbidity. Except for the aOR for mortality, death or NDI or any major morbidity in cohort A, the predictive validity measured by AUC was low to negligible. For those aOR we would expect the true value to lie between the crude and the adjusted level, which confirm the results.[27]

The association between perinatal interventional activity and outcome has been reported before. We based our centre specific activity score on the model of the Swedish regional activity score published by Serenius et al. (2015).[10] In their study, live-born infants between 22-24 weeks GA treated in regions with high versus low activity also had lower aOR for mortality (0.43, 95% CI: 0.26-0.73) and for death or NDI (aOR: 0.48, 95% CI: 0.27-0.84) at 2.5 years corrected age. As in our study, survivors in high activity regions did not have a higher risk for any NDI (aOR: 0.63, 95% CI: 0.31-1.28). This reflects the difficulty in assessing outcome at 2 years in general and using NDI as a measure of efficacy.[28,29] Other reports between intensity of care and survival date back as far as 2004 when Hakannson et al. for the first time reported how a

proactive perinatal strategy increases the number of live births and improves the infant's postnatal condition in Sweden.[30] Rysavy et al. were also able to show a clear association between the outcome of infants receiving active care and those that did not for infants between 22-24 weeks GA, but not for those between 25-26 weeks GA.[4] A study determining the perinatal outcome for extremely preterm infants in relation to place of birth in England reported lower odds for mortality when they were born in a level 3 centre with higher perinatal activity based on staffing and activity data collected by questionnaire.[11] In 2013, an NICHD study could show that 'centre intervention rates' significantly predicted mortality rates for infants <25 weeks but not for infants ≥ 25 weeks gestation.[12] Centre intervention rates included parameters similar or identical to the ones chosen for the calculation of the activity score in this study. Using yet another version of a similar intervention score, the MOSAIC study of 2009 was able to show an association between the score and mortality for infants <26 weeks but not for infants at 26 – 27 weeks gestation.[13] Swiss centres rarely initiated intensive care below 24 weeks gestation during the study period.[6,8] This is why we chose the same GA ranges for cohorts A and B as the MOSAIC study but not as the other studies. Yet, even with the more restrictive approach we confirm the results of previous studies in infants < 26 weeks gestation.

Swiss centres classified as having "high activity" for cohort A still had a higher perinatal activity score in cohort B. In contrast to the studies reported above,[4,10–13] the resulting outcome variability in cohort B is congruent to the variability in cohort A. As variability in mortality in cohort B was exclusively observed in NICU- but not in delivery room-mortality, it is difficult to determine an association to either higher perinatal activity or quality of care, or a combination of both. Arguments exist for each: centres of the high activity group also have a higher perinatal activity score in cohort B and the continuous perinatal activity score reduces risk of mortality per each 5-point increase in activity score. As variability in mortality in cohort B exists exclusively for NICU and not for delivery room mortality, variability in the decision-making process

regarding redirection of care based on futility may exist. On the other hand, centres with a high perinatal activity also had a significantly lower aOR for any major morbidities which would favour the assumption of difference in quality of care. This would be in line with the observations by Smith et al. whose findings suggest that the approach taken with infants at the limits of viability is associated with improved outcomes of more-mature infants.[31]

As reported in other studies,[10,32] median age at death was higher in high activity centres. Serenius et al. argue that the longer duration of life allows for a trial of life, whereas Costeloe et al. see the reason in different principle causes of death with a tendency towards later complications of prematurity in the case of the group of infants dying later.[10,32] Figure 3 displays that the age at death for both cohorts are comparable in their interquartile range but, together with the longer median length of stay for all infants, indicate an added burden to infants who ultimately do not survive in high activity centres.

Conclusions

A 5-point increase in perinatal interventional activity significantly decreases the aOR for mortality of infants born 22-25 weeks gestation in Switzerland. High activity centres have a significantly lower aOR for mortality and death or NDI and outcome among survivors at 2 years of age is comparable. The effect observed was repeated for infants between 26-27 weeks gestation, indicating that all extremely preterm infants benefited. Age at death and duration of hospitalization are higher suggesting a higher burden for patients who ultimately do not survive in high activity centres. Although the results favour the high activity approach, further research is required to better estimate the accompanying added burden on the children. Outcome data at 5 years of age or later are urgently required to confirm these findings with a more predictive long-term assessment.

Acknowledgements

We gratefully thank all children and their parents who participated in this study.

We also thank the following members of the Swiss Neonatal Network & Follow-Up Group for their non-author contributors:

Aarau: Cantonal Hospital Aarau, Children's Clinic, Department of Neonatology (Ph. Meyer, C. Anderegg), Department of Neuropaediatrics (A. Capone Mori, D. Kaeppeli); Basel: University of Basel Children's Hospital (UKBB), Department of Neonatology (S. Schulzke), Department of Neuropaediatrics and Developmental Medicine (P. Weber); Bellinzona: San Giovanni Hospital, Department of Paediatrics (G.P. Ramelli, B. Goeggel Simonetti); Berne: University Hospital Berne, Department of Neonatology (M. Nelle), Department of Paediatrics (B. Wagner), Department of Neuropaediatrics (M. Steinlin, S. Grunt); Biel: Children's Hospital Wildermeth, Department of Pediatrics (M. Gebauer), Development and Paediatric Neurorehabilitation Center (R. Hassink); Chur: Children's Hospital Chur, Department of Neonatology (W. Bär), Department of Neuropaediatrics (E. Keller, Ch. Killer); Fribourg: Cantonal Hospital Fribourg, Department of Neuropaediatrics (K. Fuhrer); Geneva: Department of child and adolescent, University Hospital (HUG), Neonatology Units (R. E. Pfister), Division of Development and Growth (P. S. Hüppi, C. Borradori-Tolsa); Lausanne: University Hospital (CHUV), Department of Neonatology (J.-F. Tolsa, M. Roth-Kleiner), Department of Child Development (M. Bickle-Graz); Lucerne: Children's Hospital of Lucerne, Neonatal and Paediatric Intensive Care Unit (T. M. Berger), Department of Neuropaediatrics (T. Schmitt-Mechelke, F. Bauder); Lugano: Regional Hospital Lugano, Department of Paediatrics (V. Pezzoli); Muensterlingen: Cantonal Hospital Muensterlingen, Department of Paediatrics (B. Erkert, A. Mueller); Neuchatel: Cantonal Hospital Neuchatel, Department of Paediatrics (M. Ecoffey); St. Gallen: Cantonal Hospital St. Gallen, Department of Neonatology (A. Malzacher), Children's Hospital St. Gallen, Neonatal and Paediatric Intensive Care Unit (J. P. Micallef), Department of Child Development (A. Lang-Dullenkopf); Winterthur: Cantonal Hospital Winterthur, Department of Neonatology (L. Hegi), Social Paediatrics Center (M. von Rhein); Zurich: University Hospital Zurich (USZ), Department of Neonatology (D. Bassler, R. Arlettaz), University Children's Hospital Zurich, Department of Neonatology (V. Bernet) and Child Development Center (B. Latal, G. Natalucci); Zollikerberg: Hospital Zollikerberg, Neonatology Clinic (M. Moenkhoff).

Author Contributions

Mr. Adams performed the biostatistical evaluation and together with Dr. Natalucci was involved in study design, data collection, analysis and interpretation of the results and wrote, reviewed and revised the manuscript.
Profs. Berger and Bassler, Drs. Borradori-Tolsa, Bickle-Graz, Grunt, and Gerull, were involved in data collection, study design, analysis and interpretation of data and reviewed the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

Additional data are available by emailing mark.adams@usz.ch

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Figures

Figure 1. Study population overview

Figure 2. Odds ratios of outcome when born in a unit with high perinatal interventional activity

Legend: Odds ratios with 95% confidence interval of outcome when born in high activity units, crude or adjusted for GA, GA^2, birth weight z-score, male sex, multiple births, outborn and socio-economic status. Dotted lines represent results received when using non-imputed data. AUC: area under receiver operator characteristic (ROC) curve representing predictive validity of risk adjustment.

Figure 3. Age at death in NICU (days)

Legend: Log-transformed age at death in NICU (days) for low and high activity centres in cohort A and cohort B. Crude y-axis scale on right hand side. Violin plot: box-plot with median, interquartile range and density (width = frequency). GA: gestational age. NICU: neonatal intensive care unit.

Tables

Table 1. Baseline characteristics cohorts A / B: children with and without 2-year follow-up

	Cohort A (22 – 25 weeks GA)		**Cohort B (26 – 27 weeks GA)**	
	with FU	lost to FU	with FU	lost to FU
N	319 (88.6%)	41 (11.4%)	743 (82.9%)	153 (17.1%)
Gestational age (iqr)	25.3 (24.7 to 25.6)	25 (24.6 to 25.6)	27 (26.4 to 27.4)	27 (26.6 to 27.4)
BW z-score (iqr)	-0.1 (-0.6 to 0.4)	-0.3 (-0.6 to 0.3)	0 (-0.7 to 0.5)	0.2 (-0.5 to 0.5)
Male sex	53.9 %	48.8 %	52.9 %	56.2 %
Multiple births	22.3 %	26.8 %	26.8 %	24.8 %
Outborn	2.2 %	9.8 %	4.2 %	7.2 %
SES (iqr)	6 (5 to 8)	7 (4.2 to 10)	6 (4 to 8)	6 (4 to 8)
Activity Score (iqr)	87.5 (73.7 to 89.2)	84.1 (77.8 to 89.2)	85.8 (84.2 to 91)	88.7 (84.2 to 91)
Major morbidity	60.8 %	53.7 %	39.9 %	35 %

Legend: FU: follow-up; Iqr: interquartile range; SES: socio-economic status

Table 2. Center activity grouping cohort A (standardized ratios)

	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9
Inborn [1]	95	98	94	96	96	99	100	96	97
Full course antenatal steroids [2]	56	64	80	88	91	81	100	88	97
Caesarean section [3]	44	81	67	50	88	100	93	97	93
Obstetric activity	66	83	82	80	94	96	100	96	98
Delivery room intubation or CPAP [4]	37	40	61	83	76	83	83	93	100
Surfactant < 2 hours [5]	44	39	51	35	73	82	84	97	100
Intensive care started [6]	57	78	78	100	79	83	81	88	99
Admitted [7]	57	64	77	92	79	79	76	88	100
Neonatal activity	49	55	67	78	77	82	81	92	100
Activity score	57	68	74	78	84	88	89	93	98
Activity group	low	low	low	low	high	high	high	high	high

Legend: [1]-[3]: Key obstetric indicators; [4]-[7]: key neonatal indicators; C1 – C9: centres 1 – 9; CPAP: continuous pulmonary airway pressure.

Table 3 Low vs. high activity centres cohorts A and B

	Cohort A (22 – 25 weeks GA)		**Cohort B (26 – 27 weeks GA)**	
	low activity	high activity	low activity	high activity
N	461 (49.7%)	466 (50.3%)	554 (52.9%)	493 (47.1%)
Gestational age (iqr)	24.7 (24 to 25.3)	24.6 (23.6 to 25.3)	26.9 (26.4 to 27.4)	27 (26.4 to 27.4)
BW z-score (iqr)	-0.3 (-0.8 to 0.3)	-0.4 (-1 to 0.2)	0 (-0.7 to 0.5)	0 (-0.8 to 0.5)
Male sex	51.6 %	57.6 %	52.1 %	55.8 %
Multiple births	28.2 %	27.5 %	24.2 %	28.2 %
Outborn	3.9 %	2.1 %	5.2 %	3.4 %
SES (iqr)	6 (4 to 8)	6 (5 to 8)	6 (4 to 8)	6 (4 to 8)
Activity Score (iqr)	68.1 (68.1 to 73.7)	89.2 (87.5 to 92.7)	84.2 (83.3 to 85.8)	91 (90.2 to 92.3)
Mortality	71.4 %	51.1 %	18.2 %	10.1 %
- Died in delivery room	41.9 %	34.1 %	1.6 %	1.8 %
- NICU mortality	29.5 %	17 %	16.6 %	8.3 %
Death or NDI	78.2 %	62.9 %	30.3 %	24.6 %
Any major morbidity (survivors)	62.1 %	58.7 %	43.8 %	34.2 %
Moderate to Severe NDI (survivors)	18.3 %	18.6 %	11.9 %	14.3 %
Age at death in NICU (days) (iqr)	4 (1.5 to 10.2)	8 (1.5 to 18)	6 (3 to 14)	13 (4 to 24)
Length of stay (days) (iqr)	73.5 (4 to 101.8)	100 (63 to 120)	79 (64 to 95)	85 (72 to 97)

Legend: GA: gestational age; Iqr: interquartile range; SES: socio-economic score; NDI: neurodevelopmental impairment; NICU: neonatal intensive care unit.

Table 4. Outcome at 2 years of age (corrected)

	Cohort A	Cohort B	All infants
Survivors at 2-year Follow-up (N)	319	743	1062
Mean age at 2-year Follow-up (sd)	22.5 (3)	22.6 (3.1)	22.6 (3.1)
Outcome at 2-year Follow-up			
Favourable ND	81.5 %	86.9 %	85.3 %
Moderate-to-severe NDI	18.5 %	13.1 %	14.7 %
No developmental test performed	2.8 %	1.4 %	1.8 %
BSID-II	63 %	71.4 %	68.8 %
Mean MDI (sd)	87.3 (18.8)	89.9 (17.2)	89.2 (17.7)
Mean-PDI (sd)	85.1 (18.7)	88.1 (17.2)	87.3 (17.7)
GMDS	6.0 %	3.6 %	4.3 %
Mean GMDS w/o motor (sd)	84.2 (18.2)	83.7 (20.7)	83.9 (19.5)
Bayley-III	28.2 %	23.6 %	25.0 %
Mean cognitive composite score (sd)	98.2 (16.3)	101.4 (13.8)	100.3 (14.7)
Mean composite motor score (sd)	94.7 (15.2)	97 (13.4)	96.2 (14.0)
Cerebral palsy	7.5 %	6.1 %	6.5 %
GMFCS 1	5.0 %	4.2 %	4.4 %
GMFCS 2	1.3 %	0.8 %	0.9 %
GMFCS 3-5	0.6 %	1.1 %	0.9 %
Severe visual problems	0.0 %	0.3 %	0.2 %
Severe hearing problems	1.7 %	0.7 %	1 %

Legend: Cohort A: 22 0/7 to 25 6/7 weeks gestation; cohort B: 26 0/7 to 27 6/7 weeks gestation; BSID-II: Bayley Scales of Infant Development, 2nd ed.; BSID-III / B-III: Bayley Scales of Infant and Toddler Development, 3rd ed.; Favourable ND: favourable neurodevelopment, i.e. absence of any NDI. FU: follow-up; GMDS: Griffiths Mental Developmental Scales; GMFCS: Gross Motor Function Classification System; MDI: Mental developmental index; N: number of; PDI: Psychomotor developmental index; sd: standard deviation.

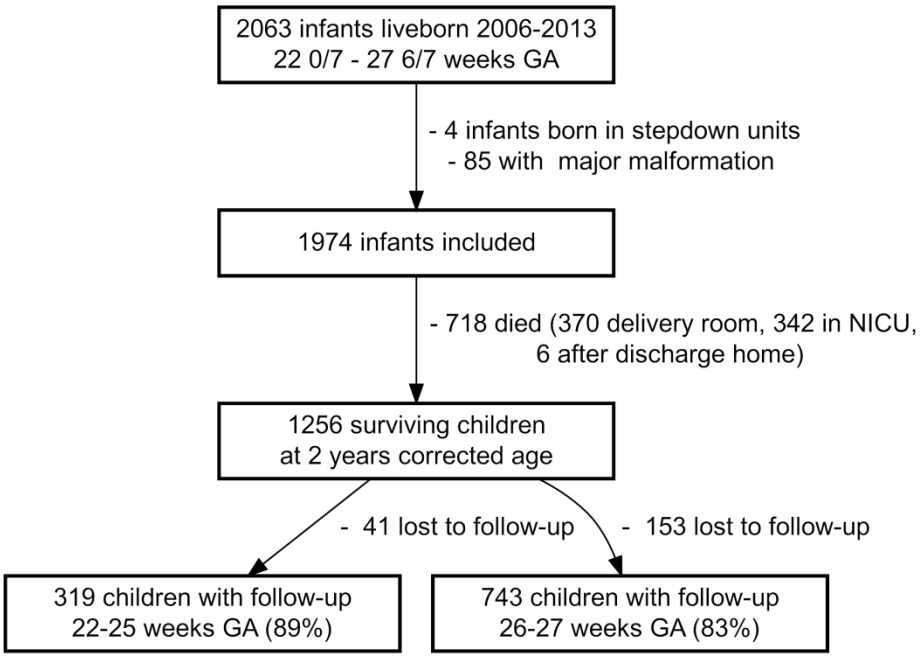
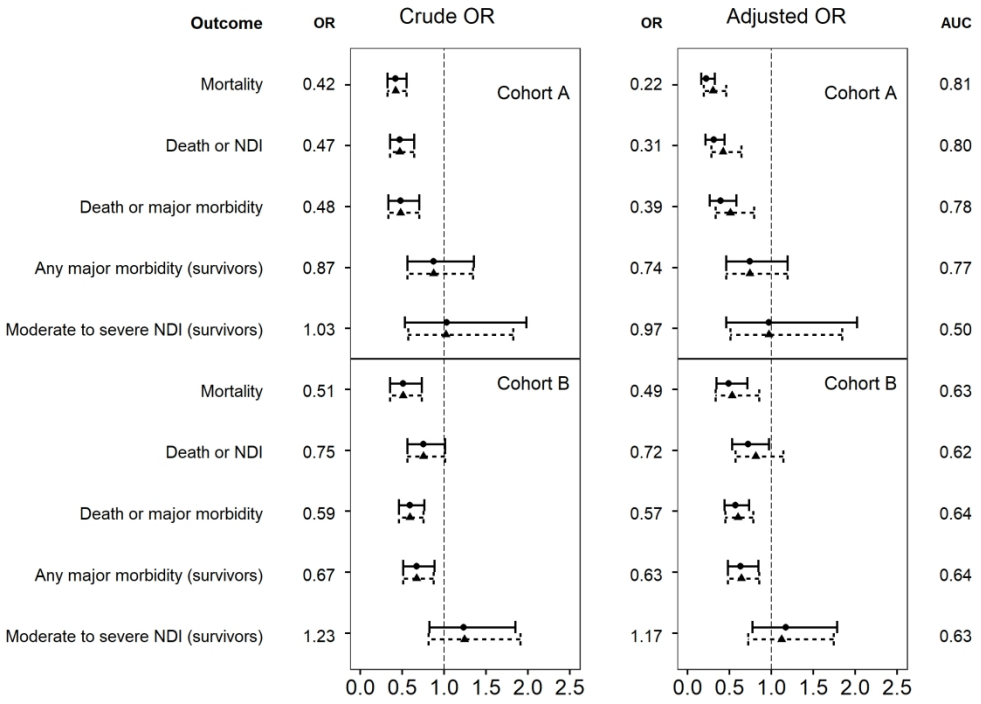


Figure 1 Study population overview



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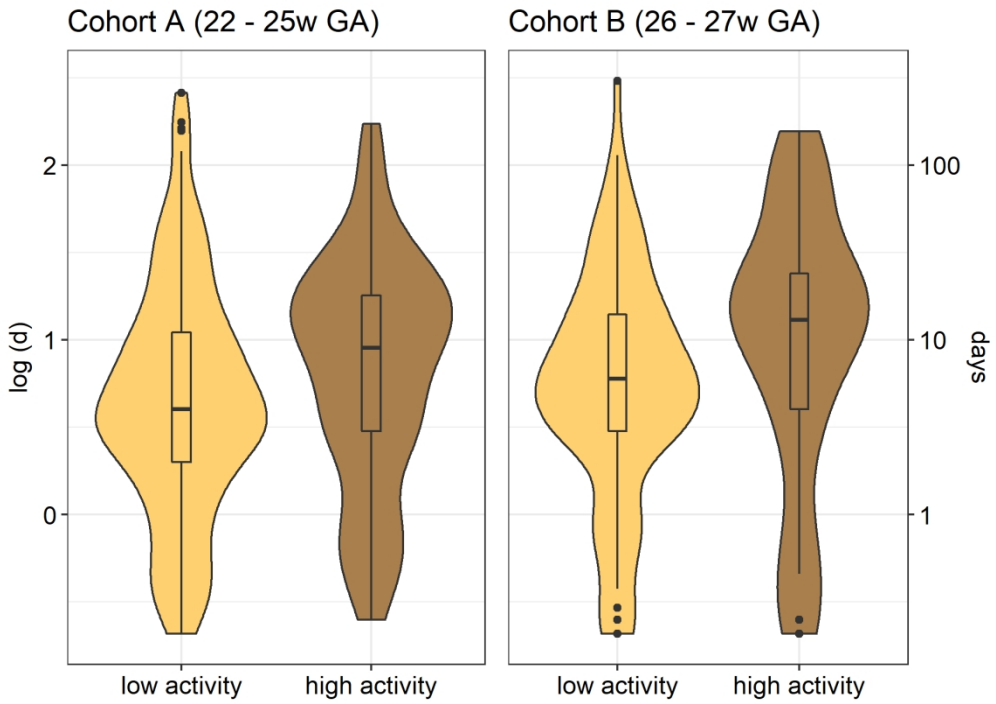

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169x119mm (300 x 300 DPI)

Supplemental table 1. Center activity grouping cohort B (standardized ratios)

	C4	C1	C2	C3	C6	C5	C7	C9	C8
Inborn [1]	94	99	98	97	95	100	100	98	100
Full course antenatal steroids [2]	74	86	90	94	88	90	86	100	84
Sectio [3]	76	88	84	80	91	100	82	89	77
Obstetric activity	84	94	94	93	94	100	92	99	90
Delivery room intubation or CPAP [4]	68	50	60	71	75	76	87	81	100
Surfactant < 2 h [5]	19	54	54	58	72	63	89	76	100
IC started [6]	100	98	99	98	99	98	98	100	100
Admitted [7]	98	100	98	99	98	98	97	100	100
Neonatal Activity	72	76	78	81	86	84	93	89	100
Activity Score	76	83	84	86	89	90	91	92	93
Activity group	low	low	low	low	high	high	high	high	high

Legend: [1]-[3]: Key obstetric indicators; [4]-[7]: key neonatal indicators; C1 – C9: centers 1 – 9; CPAP: continuous pulmonary airway pressure.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - mentioned in the abstract (design)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - done (see introduction)
Objectives	3	State specific objectives, including any prespecified hypotheses - done (see introduction)
Methods		
Study design	4	Present key elements of study design early in the paper - done (see article summary, introduction, methods)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - done (see methods)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - done (see methods – study population)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed - NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - done (see methods)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - done (see methods)
Bias	9	Describe any efforts to address potential sources of bias - done (see methods – outcome / data completeness / statistical methods)
Study size	10	Explain how the study size was arrived at - done (see methods – study population)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - done (see methods – outcome definitions / data completeness / statistical methods)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - done (see methods – statistical methods)
		(*b*) Describe any methods used to examine subgroups and interactions - done (see methods – statistical methods)
		(*c*) Explain how missing data were addressed - done (see methods – data completeness)
		(*d*) If applicable, explain how loss to follow-up was addressed - done (see methods – data completeness)
		(*e*) Describe any sensitivity analyses - done (see methods – statistical methods)

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - done (see results)
		(b) Give reasons for non-participation at each stage - done (results – study population)
		(c) Consider use of a flow diagram - done (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - done (see results, flow-chart, discussion, tables)
		(b) Indicate number of participants with missing data for each variable of interest - done (see methods – data completeness)
		(c) Summarise follow-up time (eg, average and total amount) - done (Table 4)
Outcome data	15*	Report numbers of outcome events or summary measures over time - done (see results)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - done (see methods and results)
		(*b*) Report category boundaries when continuous variables were categorized - done (see methods – perinatal interventional activity score)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - NA: cohort study setting required calculation of odds ratios.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - done (see results and discussion)
Discussion		
Key results	18	Summarise key results with reference to study objectives - done (see discussion paragraph 1)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - done (see article summary)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - done (see discussion / conclusion)
Generalisability	21	Discuss the generalisability (external validity) of the study results - done (see discussion)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - done (see declarations – competing interests)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Association between perinatal interventional activity and 2-year outcome of Swiss extremely preterm born infants: a population-based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024560.R1
Article Type:	Research
Date Submitted by the Author:	05-Oct-2018
Complete List of Authors:	Adams, Mark; Universitätsspital Zürich, Department of Neonatology; University Zurich, Epidemiology, Biostatistics and Prevention Institute Berger, Thomas; Kinderspital Luzern, Neonatal and Paediatric Intensive Care Unit Borradori-Tolsa, Cristina; Geneva University Hospital, Department of Paediatrics, Bickle-Graz, Myriam; University Hospital Lausanne, Department Woman-Mother-Child Grunt, Sebastian; Children's University Hospital, Inselspital, University of Bern, Division of Neuropaediatrics, Development and Rehabilitation Gerull, Roland; University of Basel Children's Hospital (UKBB), Department of Neonatology Bassler, Dirk; University Hospital Zurich, Department of Neonatology Natalucci, Giancarlo; UniversitatsSpital Zurich,
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	NEONATOLOGY, Fetal medicine < OBSTETRICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Association between perinatal interventional activity and 2-year outcome of Swiss extremely preterm born infants: a population-based cohort study

Mark Adams MSc[1,2,3], Professor Thomas M. Berger MD[2], Cristina Borradori-Tolsa MD[4], Myriam Bickle-Graz MD[5], Sebastian Grunt MD[6], Roland Gerull MD[7], Professor Dirk Bassler MD, MSc[1], and Giancarlo Natalucci MD[1,2,8] for the Swiss Neonatal Network & Follow-Up Group

AFFILIATIONS
[1]Department of Neonatology, University of Zurich and Zurich University Hospital, Zurich, Switzerland;
[2]Swiss Neonatal Network & Follow-up Group, Zurich, Switzerland;
[3]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland;
[4]Department of Paediatrics, Geneva University Hospital, Geneva, Switzerland;
[5]Clinic of Neonatology, Department Woman-Mother-Child, University Hospital Lausanne, Lausanne, Switzerland;
[6]Division of Neuropaediatrics, Development and Rehabilitation, Children's University Hospital, Inselspital, University of Bern, Bern, Switzerland;
[7]Department of Neonatology, University of Basel Children's Hospital (UKBB), Basel, Switzerland;
[8]Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland.

CORRESPONDING AUTHOR
Mark Adams, Department of Neonatology, University Hospital Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland; Tel. +4144 556 3034; mark.adams@usz.ch.

Short title

Perinatal intervention activity affects 2-year outcome

Financial Disclosure Statement

Mark Adams receives a salary as network coordinator for the Swiss Neonatal Network. Giancarlo Natalucci received financial support by the Swiss National Science Foundation; grant PZOOP3_161146. The remaining authors have indicated they have no financial relationships relevant to this article to disclose.

Funding

The authors received no specific funding for this work. The sponsors were not involved in the following matters: study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the manuscript for publication.

Conflict of Interest Statement

Potential Conflicts of Interest: Mark Adams receives a salary as network coordinator for the Swiss Neonatal Network. The remaining authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

List of abbreviations

aOR: adjusted odds ratio; AUC: area under receiver operator characteristic (ROC) curve; BSIDII: Bayley Scales of Infant Development, second edition; Bayley-III: Bayley Scales of Infant and Toddler Development, Third edition; BPD: bronchopulmonary dysplasia; CI: confidence interval; cPVL: cystic periventricular leukomalacia; GA: gestational age; GMDS: Griffith scales of Infant Development; GMFCS: Gross Motor Function Classification System; IVH: intraventricular haemorrhage; LOS: late onset sepsis; NDI: neurodevelopment impairment; NEC: necrotizing enterocolitis; NICHD NRN: national institute of child health neonatal research network; ROP: retinopathy of prematurity; SD: standard deviation; SES: socio-economic status; SNN: Swiss Neonatal Network & Follow-up Group.

ABSTRACT

Objectives: To investigate if centre-specific levels of perinatal interventional activity were associated with neonatal and neurodevelopmental outcome at two years of age in two separately analysed cohorts of infants: cohort A born at 22 to 25, and cohort B born at 26 to 27 gestational weeks, respectively.

Design: Geographically defined, retrospective cohort study.

Setting: All nine level III perinatal centres (neonatal intensive care units (NICUs) and affiliated obstetrical services) in Switzerland.

Patients: All live-born infants in Switzerland in 2006-2013 below 28 gestational weeks, excluding infants with major congenital malformation.

Outcome measures: Outcomes at 2 years corrected for prematurity were mortality, survival with any major neonatal morbidity, and with severe-to-moderate neurodevelopmental impairment (NDI).

Results: Cohort A associated birth in a centre with high perinatal activity with low mortality (aOR: 0.22; 95% confidence interval: 0.16-0.32), while no association was observed with survival with major morbidity (aOR: 0.74; 95% confidence interval: 0.46-1.19), and with NDI (aOR: 0.97; 95% confidence interval: 0.46-2.02). Median age at death (8 versus 4 days) and length of stay (100 versus 73 days) were higher in high than in low activity centres. The results for cohort B mirrored those for cohort A.

Conclusions: Centres with high perinatal activity in Switzerland have a significantly lower risk for mortality while having comparable outcomes among survivors. This confirms results of other studies but in a geographically defined area applying a more restrictive approach to initiation of perinatal intensive care than previous studies. The study adds that infants up to 28 weeks benefited from a higher perinatal activity and why further research is required to better estimate the added burden on children who ultimately do not survive.

Strengths and limitations of this study

- Geographically defined cohort study comparing 2-year outcome of extremely preterm infants between hospitals with high and low perinatal interventional activity based on a quantitative score of 3 obstetric and 4 neonatal indicators.
- Crude and risk-adjusted odds ratios for outcome between high and low activity centres were calculated using regression models and measuring predictive validity of risk adjustment.
- Missing outcome data of surviving infants lost to follow-up were addressed by multiple imputation and the validity of data imputation was tested by sensitivity analysis using non-imputed data.
- The interrelatedness of some of the perinatal activity score components (e.g. surfactant and respiratory support) form a limitation. However, our aim was to quantify activity and not measure quality of care. As such, the components quantify at best the level of

proactive care by focusing on the whole repertoire of first perinatal supportive interventions.

- Further minor limitations are represented by the composite nature of the outcome measures "any major morbidity" and "neurodevelopmental impairment", which could have led to a loss of information.

Keywords
Extremely preterm, limit of viability, perinatal intervention, mortality, morbidity, 2 year outcome

Word count
3239

INTRODUCTION

Over recent decades, progress in perinatal care has led to vastly improved survival rates for infants born at extremely low gestational age (GA). Consequently, the GA limit for initiating life-sustaining intensive care at birth was lowered to 22 weeks, below which treatment is generally not recommended.[1] This however raised ethical concerns regarding the added burden to infants who ultimately do not survive and the increased risk of neurosensory impairment among those that do survive.[2] There is little consensus about the policy of treating these infants. Instead, hospital practices regarding the initiation of intensive care have dramatically influenced rates of survival and survival without impairment.[3] This has led to large outcome variation among hospitals. In 2015, Rysavy et al. quantified the effect of perinatal interventional activity on outcome between a group of 24 centres of the NICHD NR network in the United States. Among infants born at 22-23 weeks gestation, centre rates of active treatment accounted for 78% of the variation in survival between centres. For those born at 24 weeks gestation it accounted for 22% of the variation.[4] There is a similar variation in decision making approaches in Europe, which appears to reflect local philosophy and practice rather than economic or demographic markers, individual variations in health expenditure or rates of preterm birth.[5] Swiss obstetricians and neonatologists are known to be generally restrictive with regards to initiation of intensive care for infants at the limit of viability. A recent study revealed that the decision-making regarding initiation of treatment was based almost exclusively on gestational age (GA) and that most infants born < 24 weeks gestation received a priori comfort care.[6] Nevertheless, centre-to-centre outcome variability has repeatedly been reported and is assumed to be in part associated with the local ethical decision making.[7–9] What remained unclear was whether the lower mortality in some centres lead to higher risk of neurodevelopmental impairment (NDI) in survivors.

This study aimed to quantify the outcome differences between centres with a higher propensity towards providing active perinatal care at birth from those that provide more a priori comfort

care. We assessed infants in cohort A (22+0 to 25+6 weeks gestational age (GA)) and compared their outcome variability with that in cohort B (26+0 to 27+6 weeks GA) where we expected no difference in either perinatal care provision or outcome based on previous studies.[4,10–13]

METHODS

Study population and procedure

Geographically defined, retrospective cohort study including all live born infants between 22+0 to 27+6 weeks of gestation in Switzerland from 2006-2013. We excluded infants born with a major congenital malformation, defined as being the primary cause of death or requiring surgery or a chromosomal anomaly. We also excluded 4 infants born and treated exclusively in 3 stepdown units. We extracted electronically recorded data (challenged for plausibility and completeness) from the prospective national database of the Swiss Neonatal Network & Follow-up Group (SNN). Data from delivery room deaths were audited by a researcher visiting the hospitals' maternity wards.

Data collection and evaluation for this study has been approved by the institutional ethical review board (KEK-ZH-Nr 2014-0552). Participating centres were obliged to inform parents about the scientific use of anonymized data.

Neonatal data

Perinatal and neonatal variables were defined as follows: GA as the best estimate available based on prenatal ultrasound examination during the first trimester of pregnancy. Birth weight z-scores, intraventricular haemorrhage grade 3 or higher (IVH), cystic periventricular leukomalacia (cPVL), bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity stages 3-4 (ROP), necrotizing enterocolitis (NEC), late onset neonatal sepsis (LOS), and Socioeconomic status (SES) were defined as previously published.[14]

Neurodevelopmental outcome at 2 years of age

Experienced neuro- or developmental paediatricians performed the standardized Swiss follow-up assessment[15] at 18-24 months corrected age in one of the Swiss follow-up centres. Between 2006 and 2012, examinations were based on Bayley Scales of Infant Development, 2. edition (BSID-II)[16] and afterwards on Bayley scales of infant and toddler development, 3. edition (Bayley-III).[17] Up until 2006, some of the children were tested using the Griffiths mental development scales-Revised (GMDS)[18] during the transition period to BSID-II. According to recent literature,[19–22] Bayley-III scores below 85 (-1SD) were considered as equivalent of indices below 70 (-2SD) in the BSID-II and the GMDS. The GMDS development quotient were considered equivalent to BSID-II MDI.[23] Infants with significant disability precluding completion of the development test were assigned a development score of 1 below -3SD. Cerebral palsy was defined according to Rosenbaum[24] and was graded according to the Gross Motor Function Classification System (GMFCS) For Children Aged ≤ 2 Years.[25] Vision and hearing were assessed by either direct examination or caregiver report.

Perinatal interventional activity score

In order to differentiate between Swiss centres with a higher propensity to initiate intensive care for infants born below 26 weeks gestation we calculated a perinatal activity score per centre based on the model presented by Serenius et al. in 2015.[10] Obstetric and neonatal activity scores reflecting the intensity of care in each centre were calculated on the basis of the rates of 3 key obstetric indicators (delivery at level III hospitals, i.e. inborn; complete course of antenatal steroids; caesarean section), and 4 key neonatal indicators (surfactant within 2 hours after birth; any of the following activities in the delivery room: bag/mask ventilation, continuous positive airway pressure, endotracheal intubation, epinephrine or adrenaline supply, cardiac compression; no recorded decision for primary non-intervention in the delivery room [available for all infants];

infants admitted for intensive care [out of infants alive at 30 minutes after birth]). The mean obstetric and neonatal activity scores comprised the perinatal activity score (henceforth, activity score). Each step included normalization by assigning the centre with the highest rate for each indicator a score of 100; the remaining centres were assigned proportional scores. We calculated an activity score for infants born between 22-25 weeks gestation (cohort A) and a separate one for infants born 26-27 weeks gestation (cohort B). The first score was used to classify the nine Swiss perinatal centres into a "low" and a "high" activity group using the arbitrary threshold of an activity score of 80 in order to generate two groups of similar size with clear difference in perinatal activity. To allow comparison between cohort A and cohort B, cohort B was split into the same centres with low and high activity as for cohort A. To confirm the dichotomous association of perinatal activity with outcome, we also tested for a linear association. For this, we generated a variable that increases by one for every 5-point increase in perinatal activity using the two perinatal activity scores for cohort A and B.

Outcome

Outcome parameters were defined as follows: mortality at 2 years corrected age, death or moderate-to-severe NDI, death or major morbidity, survival with moderate-to-severe NDI, and survival with major morbidity. Moderate-to-severe NDI was defined as either mental or motor development index below 70 (-2SD) in the BSID-II; cognitive or motor composite score below 85 (see below) in the Bayley-III; a global score of the GMDS below 70 (-2SD); cerebral palsy with GMFCS above 1; the absence of useful hearing even with aids (i.e. >90dB hearing level); blindness or only perception of light. Major morbidities encompassed IVH, cPVL, BPD, ROP, NEC or LOS.

Data completeness

Patient population coverage was assessed by comparison with the birth registry of the Swiss Federal Statistical Office and yielded 86.4% of all live births between 22-27 weeks gestation. 1.2% of the datasets were missing information on "major morbidity" and were therefore eliminated in the non-imputed analyses including this outcome. Other data was missing in less than 0.1% of cases.. As 2-year follow-up data was missing in 11% of all surviving infants between 22-25 weeks gestation and 17% between of 26-27 weeks gestation, we performed a fivefold imputation with chained equations for the cohorts A (all infants), A (survivors), B (all infants) and B (survivors), respectively, allowing the calculation of pooled adjusted odds ratios (aOR) for the above listed outcomes.[26] Data for imputation were determined as missing at random. As a sensitivity analysis, we performed the same tests with crude, i.e. non-imputed data. As outborn infants were by concept unevenly distributed between high and low activity centers, they cannot be assumed to missing at random for the imputation. We therefore performed another sensitivity analysis excluding all outborn infants for both the activity score as well as for the regression analysis.

Statistical analysis

We performed multivariable adjusted logistic regression to compare outcome between centres with lower and higher perinatal activity. Adjustment was made for GA and GA^2 (as the combination better models the non-linear dependency of most neonatal outcomes on GA and therefore results in risk adjustment with higher predictive validity), birth weight z-score, male sex, multiple births, and socio-economic status. To estimate the validity of the adjustment, we calculated how well the variables listed above predicted outcome. If this predicted validity is low, the adjustment made has limited explanatory power.[27] We calculated the area under receiver operating characteristics curve (AUC). AUC values between 0.7-0.8 were considered to

represent moderate, and >0.8 to represent high predictive validity, respectively. All statistical analyses were performed using R Version 3.4.[28]

RESULTS

Study population and neonatal data

A total of 2063 infants were born alive in Switzerland between 2006 and 2013 (Figure 1). 1839 of those infants were registered by SNN between 2007 to 2013. They correspond to 1900 life-births registered at the Swiss Federal Statistical Office in the same time period which results in a population coverage of 97% for the study period (reference data for 2006 were not available as GA was not included in the national register prior to 2007). Of the 2063 infants we excluded 4 infants because they were born in and treated at 3 stepdown units and 85 infants because of major congenital malformations. Among the 1974 included infants, 712 (36%) died before discharge and 6 (0.3%) after discharge but before reaching two years of age. In cohorts A and B, 319 (89% of survivors) and 743 (83%) were assessed at 2 years corrected age, respectively. 194 (15%) children were lost to follow-up (109 refused follow-up, 57 could not be reached/moved away, 28 unknown loss to follow-up). In both cohorts, difference between baseline characteristics of children with and without follow-up was negligible (Table 1), particularly concerning the factor "activity score" which determines the comparison groups for the subsequent analysis. Outborn children were less frequently assessed in both cohorts.

Perinatal interventional activity score

Table 2 displays the proportion of infants receiving either of the treatments determining the obstetrical activity (items [1] – [3]) and the neonatal activity (items [4] – [7]) for cohort A in each centre. Activity scores were determined out of the mean of the obstetric and neonatal activity scores and ranged from 57 to 98. Four centres with an activity score < 80 were classified as "low activity centres" encompassing 461 infants in cohort A and 554 in cohort B. The

remaining five centres were classified as "high activity centres" and combined 466 infants in cohort A and 493 in cohort B. A separate centre specific activity score was determined for cohort B using the same routine (supplemental Table 1). Each 5-point increase in perinatal activity score reduced the risk for mortality within two years of life for cohort A (aOR: 0.74, 95% confidence interval [CI] 0.68-0.80) and cohort B (aOR: 0.82, 95% CI 0.70 to 0.97).

After risk adjustment, the aOR in cohort A for mortality (0.22, 95% CI 0.15-0.31) and death or NDI (0.30, 95% CI 0.21-0.42) were significantly lower (Figure 2) for high compared to low activity centres. After restricting the cohort to survivors, aOR for any major neonatal morbidities was 0.75 (95% CI 0.47-1.19) and for moderate to severe NDI 0.95 (95% CI 0.46-1.98). The crude baseline characteristics of low versus high activity centres in cohort A (Table 3) were comparable for size, GA range, birth weight z-score, multiple births and SES. However, High activity centres had more male infants and less outborn infants. The crude outcome proportions reflect the aOR results. Repeating the same evaluation using non-imputed data resulted in almost the same point-estimates and confidence intervals (dotted lines in Figure 2). As outborn infants were unevenly distributed between children with and without follow-up, we repeated the analysis excluding all 75 outborn infants from the beginning for both the activity score and the regression analysis. The resulting aOR were almost equivalent to the ones reported above (supplemental Figure 1). Excluding the delivery room deaths, median NICU age at death in high activity centres was higher (8 versus 4 days) as was length of stay (100 versus 73 days). As can be seen in Figure 3, the distribution of age at death was different between high and low activity centres. In high activity centres, the highest density was reached above the median, whereas it was below the median in low activity centres. The violin plot thereby allows taking the full distribution of the data into account rather than relying on median and interquartile range alone.

Centres classified as having "high activity" for cohort A, still had a higher perinatal activity score (91 vs. 84) in cohort B with matching outcome variability. aOR for mortality (0.49, 95% CI 0.34-0.71) and death or NDI (0.72, 95% CI 0.53-0.97) were significantly lower in high activity centres (Figure 2). In contrast to cohort A the aOR for any major morbidities was also significantly lower (0.63, 95% CI 0.48-0.84) whereas moderate to severe NDI outcome in survivors was higher without reaching significance (1.17, 95% CI 0.77-1.78). Again, crude baseline characteristics (Table 3) were comparable with more male and fewer outborn infants in high activity centres. Crude outcomes mirror the aOR result. In cohort B, median age at death in NICU in high activity centres was again higher (11 versus 6 days), whereas length of stay was only somewhat longer (85 versus 78 days).

Neurodevelopmental outcome at 2 years of age

Follow-up assessment was performed at a mean (SD) corrected age of 22.6 (3.1) months (Table 4). Of 1062 examined children, 729 (69%), 265 (25%), and 46 (4%) were assessed with the Bayley-II, Bayley-III, and GMDS, respectively while in 19 (2%) children only a part of a developmental assessment could be performed because of severe cerebral palsy or poor compliance. 220 (21%) infants suffered from moderate-to-severe NDI and 842 (79%) infants showed favourable outcome.

DISCUSSION

Swiss perinatal centres with a higher score of perinatal activity for infants at the borderline of viability (cohort A) had significantly lower aOR for mortality and for the composite outcome death or NDI. After restricting the cohort to survivors at two years of age corrected for prematurity, there was no significant difference between centres with high and low intensity regarding risk for major morbidity or NDI. Cohort B mirrored the outcome differences between high and low activity perinatal centres determined for cohort A, i.e. significantly lower aOR for

mortality and for death or NDI. In contrast to cohort A, the lower mortality in high activity centres in cohort B was based exclusively on NICU mortality. High activity centres in cohort B had a significantly lower aOR for any major neonatal morbidity. Except for the aOR for mortality, death or NDI or any major morbidity in cohort A, the predictive validity measured by AUC was low to negligible. For those aOR we would expect the true value to lie between the crude and the adjusted level, which confirm the results.[29]

The association between perinatal interventional activity and outcome has been reported before. We based our centre specific activity score on the model of the Swedish regional activity score published by Serenius et al. (2015).[10] In their study, live-born infants between 22-24 weeks GA treated in regions with high versus low activity also had lower aOR for mortality (0.43, 95% CI: 0.26-0.73) and for death or NDI (aOR: 0.48, 95% CI: 0.27-0.84) at 2.5 years corrected age. As in our study, survivors in high activity regions did not have a higher risk for any NDI (aOR: 0.63, 95% CI: 0.31-1.28). This reflects the difficulty in assessing outcome at 2 years in general and using NDI as a measure of efficacy.[30,31] Other reports between intensity of care and survival date back as far as 2004 when Hakannson et al. for the first time reported how a proactive perinatal strategy increases the number of live births and improves the infant's postnatal condition in Sweden.[32] Rysavy et al. were also able to show a clear association between the outcome of infants receiving active care and those that did not for infants between 22-24 weeks GA, but not for those between 25-26 weeks GA.[4] A study determining the perinatal outcome for extremely preterm infants in relation to place of birth in England reported lower odds for mortality when they were born in a level 3 centre with higher perinatal activity based on staffing and activity data collected by questionnaire.[11] In 2013, an NICHD study could show that 'centre intervention rates' significantly predicted mortality rates for infants <25 weeks but not for infants ≥ 25 weeks gestation.[12] Centre intervention rates included parameters similar or identical to the ones chosen for the calculation of the activity score in this study. Using

yet another version of a similar intervention score, the MOSAIC study of 2009 was able to show an association between the score and mortality for infants <26 weeks but not for infants at 26 – 27 weeks gestation.[13] Swiss centres rarely initiated intensive care below 24 weeks gestation during the study period.[6,8] This is why we chose the same GA ranges for cohorts A and B as the MOSAIC study but not as the other studies. Yet, even with the more restrictive approach we confirm the results of previous studies in infants < 26 weeks gestation.

Swiss centres classified as having "high activity" for cohort A still had a higher perinatal activity score in cohort B. In contrast to the studies reported above,[4,10–13] the resulting outcome variability in cohort B is congruent to the variability in cohort A. As variability in mortality in cohort B was exclusively observed in NICU- but not in delivery room-mortality, it is difficult to determine an association to either higher perinatal activity or quality of care, or a combination of both. Arguments exist for each: centres of the high activity group also have a higher perinatal activity score in cohort B and the continuous perinatal activity score reduces risk of mortality per each 5-point increase in activity score. As variability in mortality in cohort B exists exclusively for NICU and not for delivery room mortality, variability in the decision-making process regarding redirection of care based on futility may exist. On the other hand, centres with a high perinatal activity also had a significantly lower aOR for any major morbidities which would favour the assumption of difference in quality of care. This would be in line with the observations by Smith et al. whose findings suggest that the approach taken with infants at the limits of viability is associated with improved outcomes of more-mature infants.[33]

As reported in other studies,[10,34] median age at death was higher in high activity centres. Serenius et al. argue that the longer duration of life allows for a trial of life, whereas Costeloe et al. see the reason in different principle causes of death with a tendency towards later complications of prematurity in the case of the group of infants dying later.[10,34] Figure 3

displays that the age at death for both cohorts are comparable in their interquartile range but, together with the longer median length of stay for all infants, indicate an added burden to infants who ultimately do not survive in high activity centres.

Conclusions

A 5-point increase in perinatal interventional activity significantly decreases the aOR for mortality of infants born 22-25 weeks gestation in Switzerland. High activity centres have a significantly lower aOR for mortality and death or NDI and outcome among survivors at 2 years of age is comparable. The effect observed was repeated for infants between 26-27 weeks gestation, indicating that all extremely preterm infants benefited. Age at death and duration of hospitalization are higher suggesting a higher burden for patients who ultimately do not survive in high activity centres. Although the results favour the high activity approach, further research is required to better estimate the accompanying added burden on the children. Outcome data at 5 years of age or later are urgently required to confirm these findings with a more predictive long-term assessment.

Acknowledgements

We gratefully thank all children and their parents who participated in this study.

We also thank the following members of the Swiss Neonatal Network & Follow-Up Group for their non-author contributors:

Aarau: Cantonal Hospital Aarau, Children's Clinic, Department of Neonatology (Ph. Meyer, C. Anderegg), Department of Neuropaediatrics (A. Capone Mori, D. Kaeppeli); Basel: University of Basel Children's Hospital (UKBB), Department of Neonatology (S. Schulzke), Department of Neuropaediatrics and Developmental Medicine (P. Weber); Bellinzona: San Giovanni Hospital, Department of Paediatrics (G.P. Ramelli, B. Goeggel Simonetti); Berne: University Hospital Berne, Department of Neonatology (M. Nelle), Department of Paediatrics (B. Wagner), Department of Neuropaediatrics (M. Steinlin, S. Grunt); Biel: Children's Hospital Wildermeth, Department of Pediatrics (M. Gebauer), Development and Paediatric Neurorehabilitation Center (R. Hassink); Chur: Children's Hospital Chur, Department of Neonatology (W. Bär), Department of Neuropaediatrics (E. Keller, Ch. Killer); Fribourg: Cantonal Hospital Fribourg, Department of Neuropaediatrics (K. Fuhrer); Geneva: Department of child and adolescent, University Hospital (HUG), Neonatology Units (R. E. Pfister), Division of Development and Growth (P. S. Hüppi, C. Borradori-Tolsa); Lausanne: University Hospital (CHUV), Department of Neonatology (J.-F. Tolsa, M. Roth-Kleiner), Department of Child Development (M. Bickle-Graz); Lucerne: Children's Hospital of Lucerne, Neonatal and Paediatric Intensive Care Unit (T. M. Berger), Department of Neuropaediatrics (T. Schmitt-Mechelke, F. Bauder); Lugano: Regional Hospital Lugano, Department of Paediatrics (V. Pezzoli); Muensterlingen: Cantonal Hospital Muensterlingen, Department of Paediatrics (B. Erkert, A. Mueller); Neuchatel: Cantonal Hospital Neuchatel, Department of Paediatrics (M. Ecoffey); St. Gallen: Cantonal Hospital St. Gallen, Department of Neonatology (A. Malzacher), Children's Hospital St. Gallen, Neonatal and Paediatric Intensive Care Unit (J. P. Micallef), Department of Child Development (A. Lang-Dullenkopf); Winterthur: Cantonal Hospital Winterthur, Department of Neonatology (L. Hegi), Social Paediatrics Center (M. von Rhein); Zurich: University Hospital Zurich (USZ), Department of Neonatology (D. Bassler, R. Arlettaz), University Children's Hospital Zurich, Department of Neonatology (V. Bernet) and Child Development Center (B. Latal, G. Natalucci); Zollikerberg: Hospital Zollikerberg, Neonatology Clinic (M. Moenkhoff).

Author Contributions

Mr. Adams performed the biostatistical evaluation and together with Dr. Natalucci was involved in study design, data collection, analysis and interpretation of the results and wrote, reviewed and revised the manuscript.
Profs. Berger and Bassler, Drs. Borradori-Tolsa, Bickle-Graz, Grunt, and Gerull, were involved in data collection, study design, analysis and interpretation of data and reviewed the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

Additional data are available by emailing mark.adams@usz.ch

Patient and Public Involvement

Patients or public were not involved in the development of the research question, the outcome measures or the study design. The results of this study will be disseminated to study participants, as well as to other patients, through the patient and public page of the Swiss neonatal and follow-up website.

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Figures

Figure 1. Study population overview

Figure 2. Odds ratios of outcome when born in a unit with high perinatal interventional activity

Legend: Odds ratios with 95% confidence interval of outcome when born in high activity units, crude or adjusted for GA, GA^2, birth weight z-score, male sex, multiple births, and socio-economic status. Dotted lines represent results received when using non-imputed data. AUC: area under receiver operator characteristic (ROC) curve representing predictive validity of risk adjustment.

Figure 3. Age at death in NICU (days)

Legend: Log-transformed age at death in NICU (days) for low and high activity centres in cohort A and cohort B. Crude y-axis scale on right hand side. Violin plot: box-plot with median, interquartile range and density (width = frequency). GA: gestational age. NICU: neonatal intensive care unit.

Tables

Table 1. Baseline characteristics cohorts A / B: children with and without 2-year follow-up

	Cohort A (22 – 25 weeks GA)		**Cohort B (26 – 27 weeks GA)**	
	with FU	lost to FU	with FU	lost to FU
N	319 (88.6%)	41 (11.4%)	743 (82.9%)	153 (17.1%)
Gestational age (iqr)	25.3 (24.7 to 25.6)	25 (24.6 to 25.6)	27 (26.4 to 27.4)	27 (26.6 to 27.4)
BW z-score (iqr)	-0.1 (-0.6 to 0.4)	-0.3 (-0.6 to 0.3)	0 (-0.7 to 0.5)	0.2 (-0.5 to 0.5)
Male sex	53.9 %	48.8 %	52.9 %	56.2 %
Multiple births	22.3 %	26.8 %	26.8 %	24.8 %
Outborn	2.2 %	9.8 %	4.2 %	7.2 %
SES (iqr)	6 (5 to 8)	7 (4.2 to 10)	6 (4 to 8)	6 (4 to 8)
Activity Score (iqr)	87.5 (73.7 to 89.2)	84.1 (77.8 to 89.2)	85.8 (84.2 to 91)	88.7 (84.2 to 91)
Major morbidity	60.8 %	53.7 %	39.9 %	35 %

Legend: FU: follow-up; Iqr: interquartile range; SES: socio-economic status was calculated by means of a score reflecting both maternal education an paternal occupation, with a maximum and minimum scores of 12 and 2, indicating lower and higher status, respectively.

Table 2. Center activity grouping cohort A (standardized ratios)

	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	Highest Proportion*
Inborn [1]	95	98	94	96	96	99	100	96	97	100%
Full course antenatal steroids [2]	56	64	80	88	91	81	100	88	97	51.5%
Caesarean section [3]	44	81	67	50	88	100	93	97	93	60.7%
Obstetric activity	66	83	82	80	94	96	100	96	98	-
Delivery room intubation or CPAP [4]	37	40	61	83	76	83	83	93	100	71.9%
Surfactant < 2 hours [5]	44	39	51	35	73	82	84	97	100	65.6%
Intensive care started [6]	57	78	78	100	79	83	81	88	99	81.7%
Admitted [7]	57	64	77	92	79	79	76	88	100	81.2%
Neonatal activity	49	55	67	78	77	82	81	92	100	-
Activity score	57	68	74	78	84	88	89	93	98	-
Activity group	low	low	low	Low	high	high	high	high	high	-

Legend: [1]-[3]: Key obstetric indicators; [4]-[7]: key neonatal indicators; C1 – C9: centres 1 – 9; CPAP: continuous pulmonary airway pressure.*Highest proportion: actual proportion of infants receiving intervention in center with highest incidence, standardized as 100 in activity score.

Table 3 Low vs. high activity centres cohorts A and B

	Cohort A (22 – 25 weeks GA)		Cohort B (26 – 27 weeks GA)	
	low activity	high activity	low activity	high activity
N	461 (49.7%)	466 (50.3%)	554 (52.9%)	493 (47.1%)
Gestational age (iqr)	24.7 (24 to 25.3)	24.6 (23.6 to 25.3)	26.9 (26.4 to 27.4)	27 (26.4 to 27.4)
BW z-score (iqr)	-0.3 (-0.8 to 0.3)	-0.4 (-1 to 0.2)	0 (-0.7 to 0.5)	0 (-0.8 to 0.5)
Male sex	51.6 %	57.6 %	52.1 %	55.8 %
Multiple births	28.2 %	27.5 %	24.2 %	28.2 %
Outborn	3.9 %	2.1 %	5.2 %	3.4 %
SES (iqr)	6 (4 to 8)	6 (5 to 8)	6 (4 to 8)	6 (4 to 8)
Activity Score (iqr)	68.1 (68.1 to 73.7)	89.2 (87.5 to 92.7)	84.2 (83.3 to 85.8)	91 (90.2 to 92.3)
Mortality	71.4 %	51.1 %	18.2 %	10.1 %
- Died in delivery room	41.9 %	34.1 %	1.6 %	1.8 %
- NICU mortality	29.5 %	17 %	16.6 %	8.3 %
Death or NDI	78.2 %	62.9 %	30.3 %	24.6 %
Any major morbidity (survivors)	62.1 %	58.7 %	43.8 %	34.2 %
Moderate to Severe NDI (survivors)	18.3 %	18.6 %	11.9 %	14.3 %
Age at death in NICU (days) (iqr)	4 (1.5 to 10.2)	8 (1.5 to 18)	6 (3 to 14)	13 (4 to 24)
Length of stay (days) (iqr)	73.5 (4 to 101.8)	100 (63 to 120)	79 (64 to 95)	85 (72 to 97)

Legend: GA: gestational age; Iqr: interquartile range; SES: socio-economic score was calculated by means of a score reflecting both maternal education an paternal occupation, with a maximum and minimum scores of 12 and 2, indicating lower and higher status, respectively; NDI: neurodevelopmental impairment; NICU: neonatal intensive care unit.

Table 4. Outcome at 2 years of age (corrected)

	Cohort A	Cohort B	All infants
Survivors at 2-year Follow-up (N)	319	743	1062
Mean age at 2-year Follow-up (sd)	22.5 (3)	22.6 (3.1)	22.6 (3.1)
Outcome at 2-year Follow-up			
Favourable ND	81.5 %	86.9 %	85.3 %
Moderate-to-severe NDI	18.5 %	13.1 %	14.7 %
No developmental test performed	2.8 %	1.4 %	1.8 %
BSID-II	63 %	71.4 %	68.8 %
Mean MDI (sd)	87.3 (18.8)	89.9 (17.2)	89.2 (17.7)
Mean-PDI (sd)	85.1 (18.7)	88.1 (17.2)	87.3 (17.7)
GMDS	6.0 %	3.6 %	4.3 %
Mean GMDS w/o motor (sd)	84.2 (18.2)	83.7 (20.7)	83.9 (19.5)
Bayley-III	28.2 %	23.6 %	25.0 %
Mean cognitive composite score (sd)	98.2 (16.3)	101.4 (13.8)	100.3 (14.7)
Mean composite motor score (sd)	94.7 (15.2)	97 (13.4)	96.2 (14.0)
Cerebral palsy	7.5 %	6.1 %	6.5 %
GMFCS 1	5.0 %	4.2 %	4.4 %
GMFCS 2	1.3 %	0.8 %	0.9 %
GMFCS 3-5	0.6 %	1.1 %	0.9 %
Severe visual problems	0.0 %	0.3 %	0.2 %
Severe hearing problems	1.7 %	0.7 %	1 %

Legend: Cohort A: 22 0/7 to 25 6/7 weeks gestation; cohort B: 26 0/7 to 27 6/7 weeks gestation; BSID-II: Bayley Scales of Infant Development, 2nd ed.; BSID-III / B-III: Bayley Scales of Infant and Toddler Development, 3rd ed.; Favourable ND: favourable neurodevelopment, i.e. absence of any NDI. FU: follow-up; GMDS: Griffiths Mental Developmental Scales; GMFCS: Gross Motor Function Classification System; MDI: Mental developmental index; N: number of; PDI: Psychomotor developmental index; sd: standard deviation.

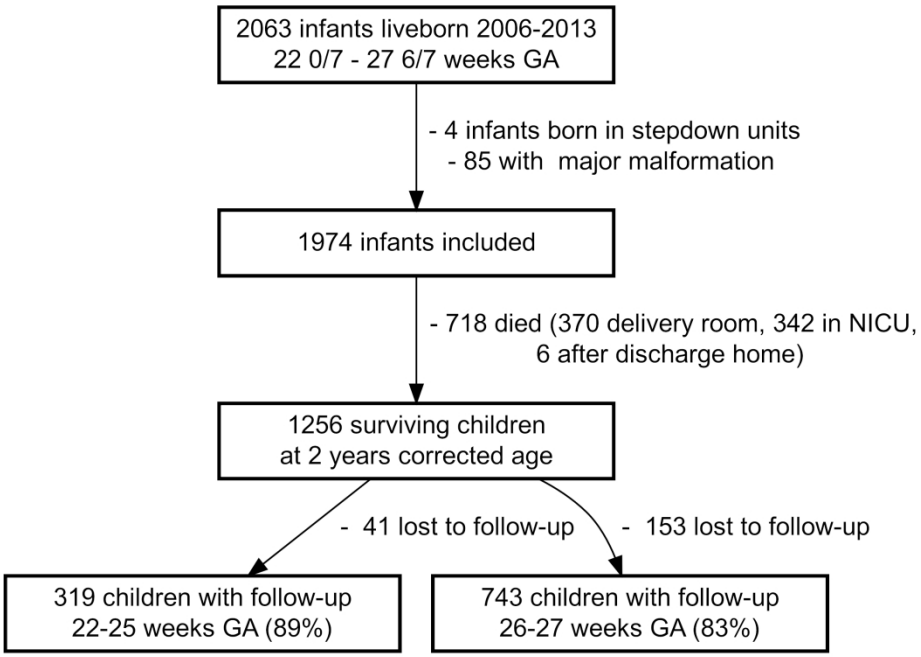

Figure 1 Study population overview

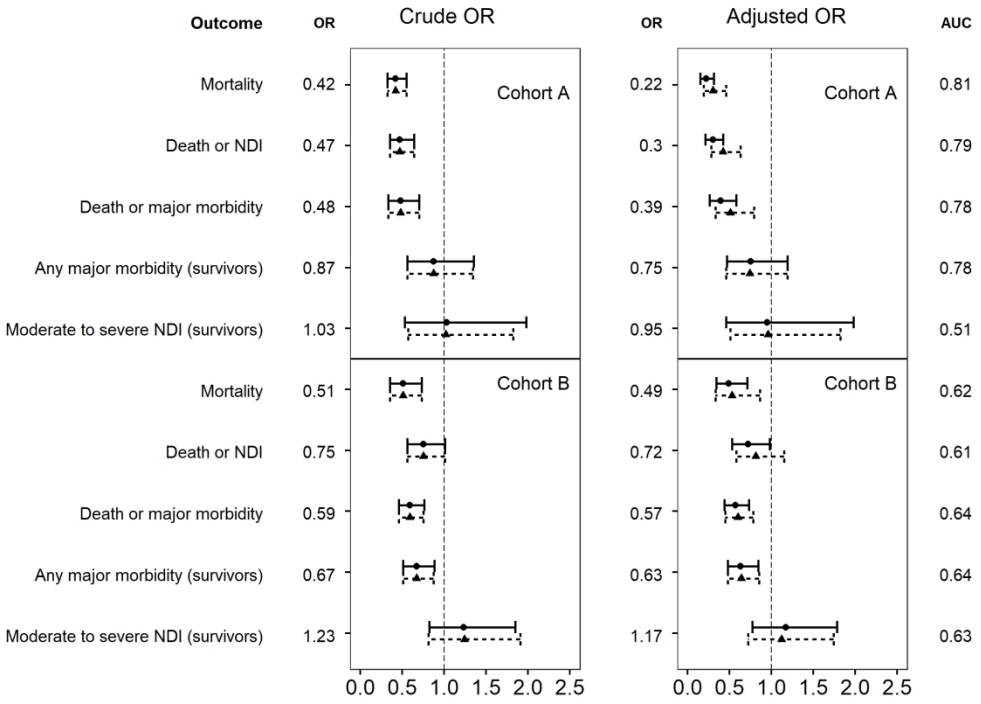

Figure 2. Odds ratios of outcome when born in a unit with high perinatal interventional activityLegend: Odds ratios with 95% confidence interval of outcome when born in high activity units, crude or adjusted for GA, GA2, birth weight z-score, male sex, multiple births, and socio-economic status. Dotted lines represent results received when using non-imputed data. AUC: area under receiver operator characteristic (ROC) curve representing predictive validity of risk adjustment.

199x149mm (300 x 300 DPI)

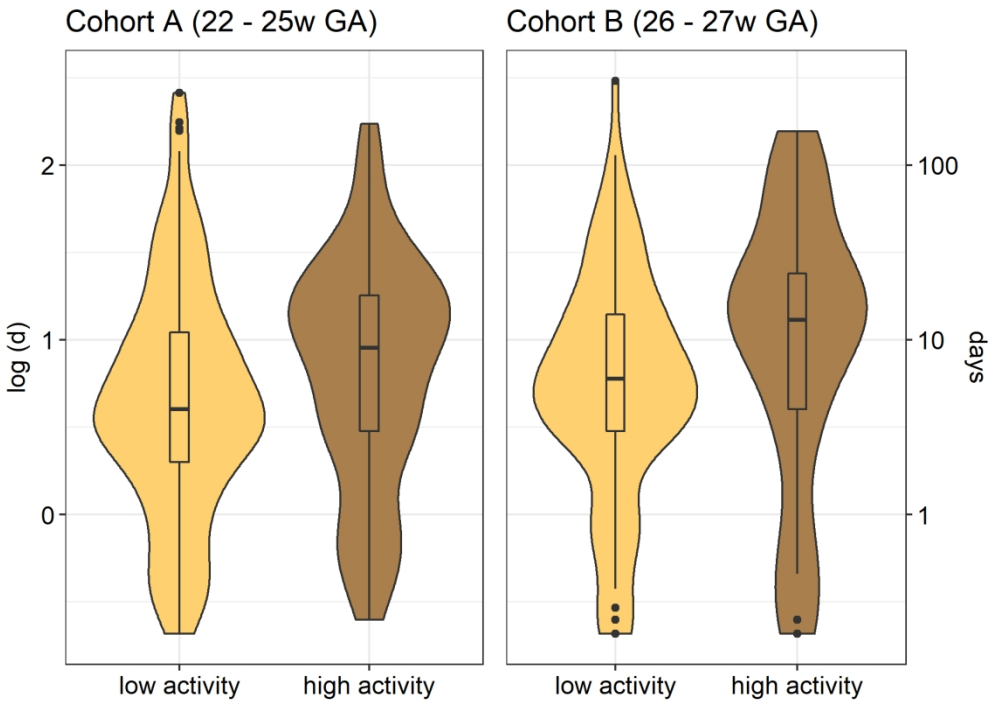

Figure 3. Age at death in NICU (days)

Legend: Log-transformed age at death in NICU (days) for low and high activity centres in cohort A and cohort B. Crude y-axis scale on right hand side. Violin plot: box-plot with median, interquartile range and density (width = frequency). GA: gestational age. NICU: neonatal intensive care unit.

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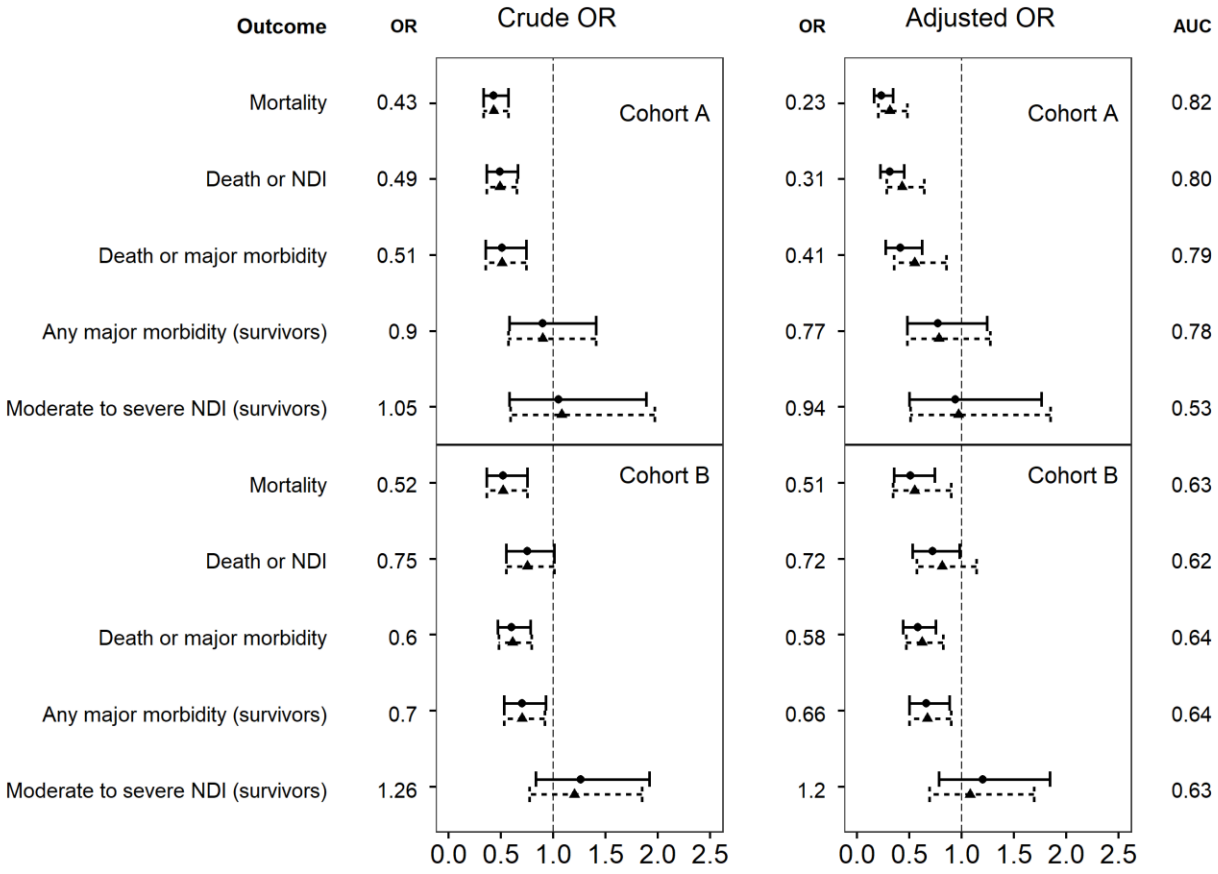
Supplemental table 1. Center activity grouping cohort B (standardized ratios)

	C4	C1	C2	C3	C6	C5	C7	C9	C8	Highest Proportion*
Inborn [1]	94	99	98	97	95	100	100	98	100	97.8%
Full course antenatal steroids [2]	74	86	90	94	88	90	86	100	84	80.4%
Sectio [3]	76	88	84	80	91	100	82	89	77	95.6%
Obstetric activity	84	94	94	93	94	100	92	99	90	-
Delivery room intubation or CPAP [4]	68	50	60	71	75	76	87	81	100	83.5%
Surfactant < 2 h [5]	19	54	54	58	72	63	89	76	100	77.2%
IC started [6]	100	98	99	98	99	98	98	100	100	100%
Admitted [7]	98	100	98	99	98	98	97	100	100	100%
Neonatal Activity	72	76	78	81	86	84	93	89	100	-
Activity Score	76	83	84	86	89	90	91	92	93	-
Activity group	low	low	low	low	high	high	high	high	high	-

Legend: [1]-[3]: Key obstetric indicators; [4]-[7]: key neonatal indicators; C1 – C9: centers 1 – 9; CPAP: continuous pulmonary airway pressure. *Highest proportion: actual proportion of infants receiving intervention in center with highest incidence, standardized as 100 in activity score.

Supplemental Figure 1. Odds ratios of outcome when born in a unit with high perinatal interventional activity after exclusion of all outborn infants



Legend: Odds ratios with 95% confidence interval of outcome when born in high activity units, crude or adjusted for GA, GA^2, birth weight z-score, male sex, multiple births, socio-economic status. Dotted lines represent results received when using non-imputed data. AUC: area under receiver operator characteristic (ROC) curve representing predictive validity of risk adjustment.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - mentioned in the abstract (design), p. 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - done, p. 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - done (see introduction), p. 4
Objectives	3	State specific objectives, including any prespecified hypotheses - done (see introduction), p. 5
Methods		
Study design	4	Present key elements of study design early in the paper - done (see article summary, introduction, methods), pp. 2, 4ff.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - done (see methods), pp. 5-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - done (see methods – study population), p. 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed - NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - done (see methods), pp. 5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - done (see methods), pp. 5-8
Bias	9	Describe any efforts to address potential sources of bias - done (see methods – outcome / data completeness / statistical methods), pp. 7-8
Study size	10	Explain how the study size was arrived at - done (see methods – study population), p. 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - done (see methods – outcome definitions / data completeness / statistical methods), pp. 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - done (see methods – statistical methods) p. 8
		(*b*) Describe any methods used to examine subgroups and interactions - done (see methods – statistical methods), p. 8
		(*c*) Explain how missing data were addressed - done (see methods – data completeness), p. 8
		(*d*) If applicable, explain how loss to follow-up was addressed - done (see methods – data completeness), p. 8
		(*e*) Describe any sensitivity analyses

		- done (see methods – statistical methods), p. 8
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - done (see results), pp. 9-11
		(b) Give reasons for non-participation at each stage - done (results – study population), p. 9
		(c) Consider use of a flow diagram - done (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - done (see results, flow-chart, discussion, tables), pp. 9ff.
		(b) Indicate number of participants with missing data for each variable of interest - done (see methods – data completeness), p. 8
		(c) Summarise follow-up time (eg, average and total amount) - done (Table 4), p. 26
Outcome data	15*	Report numbers of outcome events or summary measures over time - done (see results), p. 9 – 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - done (see methods and results), pp. 5 – 11
		(*b*) Report category boundaries when continuous variables were categorized - done (see methods – perinatal interventional activity score), p. 6 f.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - NA: cohort study setting required calculation of odds ratios.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - done (see results and discussion) pp. 10-11
Discussion		
Key results	18	Summarise key results with reference to study objectives - done (see discussion paragraph 1), p. 11f
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - done (see article summary), p. 2 f.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - done (see discussion / conclusion), p. 14
Generalisability	21	Discuss the generalisability (external validity) of the study results - done (see discussion), pp. 11-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - done (see declarations – competing interests), p. 1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.