

Preterm Morbidity and Mortality by Gestational Age. A Birth Population-Based Study

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Research article

Keywords: birth population, incidence, preterm morbidity and mortality, gestational age-specific, regional perinatal-neonatal network

Posted Date: August 21st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-61695/v1>

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Version of Record: A version of this preprint was published at BMC Pregnancy and Childbirth on April 10th, 2021. See the published version at <https://doi.org/10.1186/s12884-021-03726-4>.

Abstract

Background: Despite 15-17 million of annual births in China, there is a paucity of information on preterm morbidity and mortality. We characterized the outcome of preterm births and hospitalized preterm infants by gestational age (GA) in Huai'an in 2015, an emerging prefectural region of China.

Methods: Of 59,245 regional total births, clinical data on 2,651 preterm births and 1,941 hospitalized preterm neonates were extracted from Huai'an Women and Children's Hospital (HWCH) and non-HWCH hospitals in 2018-2020. Preterm morbidity and mortality rates were characterized and compared by hospital categories and GA spectra. Death risks of preterm births and hospitalized preterm infants in the whole region were analyzed with multivariable logistic regression.

Results: The incidences of extreme, very, moderate, late and total preterm of the regional total births were 1.4, 5.3, 7.2, 30.8 and 44.7‰, with all-death rates being 1.0, 1.6, 0.6, 1.1 and 4.3‰, respectively, of the regional total births. There were 1,025 (52.8% of whole region) preterm admissions in HWCH, with significantly lower in-hospital death rate of inborn (33/802) than out-born (23/223) infants. Compared to non-HWCH, four-fold more neonates in HWCH were under critical care with higher death rate, including most extremely preterm infants. Significant all-death risks were found for the total preterm births in BW < 1,000g, II-III degree of amniotic fluid contamination, Apgar-5 min \leq 7, and birth defects (BD). For the hospitalized preterm infants, significant in-hospital death risks were found in out-born of HWCH, GA < 32 weeks, Apgar-5 min \leq 7, BD, necrotizing enterocolitis and ventilation, whereas born in HWCH, antenatal glucocorticoids, cesarean delivery and surfactant use were protective factors against death.

Conclusions: The integrated data revealed GA-specific morbidity and mortality on the basis of total preterm births and their hospitalization, demonstrating the efficacy of leading referral center and whole regional perinatal-neonatal network in China. The concept and protocol of our current study should be extended to gain comprehensive understanding in the world-wide campaign for prevention of preterm birth.

Background

Perinatal and neonatal morbidity and mortality of preterm births represent the focus of quality improvement with perinatal healthcare strategies [1-5]. Despite the majority of neonatal deaths attributed to preterm birth complication, and a large amount of hospital admission-based data by gestational age (GA) available in China, the whole picture of perinatal-neonatal care remains unclear due to a lack of birth population-based clinical surveys [6-9]. Although the number of Chinese annual birth population has reached 15-17 million in the past decade, with an established universal health insurance covering maternal-infant healthcare [10-13], there is a paucity of data on vital statistics of preterm births and assessment of combined effects of antenatal, peripartum and postnatal interventions on perinatal and neonatal outcome in the preterm birth and hospitalized population.

Antenatal glucocorticoids (ANG), or glucocorticosteroids, plays a pivotal role in fetal lung maturation, and has long been demonstrated in developed settings to reduce the risk of postnatal morbidities, such as respiratory distress syndrome (RDS) and intraventricular hemorrhage (IVH) [1-5,7,8,14-15]. However, benefits of this strategy may be less profound, or even absent, in low- and middle-income countries where socioeconomic status and healthcare conditions are different [16]. In this regard, further in-depth investigations are required to unravel the safety and efficacy of ANG under particular clinical settings, in order to optimize facility-based practice in emerging regions in world-wide perspective.

The national surveillance system reporting on perinatal information in China has limitations as it only retrieved data of preterm births ≥ 28 weeks of gestational age (GA) [6,17-19]. Huai'an is an emerging prefectural region in east China with 5.6-million population with 50% rural residents, the regional gross domestic production per capita approaching the national average level. According to our previous surveys of complete birth registries in Huai'an in 2015, a survival rate of more than 50% was observed in preterm infants with 27-28 gestational weeks and beyond [11]. By comparison, the 50% survival rate was reported in 23-25 weeks of gestation from the nation-wide registry or perinatal network data in developed countries [1-5,7-9]. Our previous data demonstrated substantial and persistent improvement in Huai'an perinatal-neonatal care between 2010 and 2015, probably due to the establishment of centralized prenatal care and deliveries at level II and III hospitals [10,11,20]. This enabled us to take facility-specific conditions and regional infrastructure into consideration, when investigating the impact of integrated antenatal, peripartum and postnatal interventions in this region.

The current study aimed to depict the morbidity and mortality of whole regional preterm births and hospitalized infants stratified by GA, investigate the role of Huai'an Women and Children's Hospital (HWCH) as the main transferal center of whole region, and verify the efficacy of perinatal interventions and the underlying neonatal morbidities of deaths. As birth population-based studies on perinatal and neonatal healthcare are still at preliminary stage in China [6,12,13], our concept and methodology of using regional birth registry data to assess death risks in hospitalized preterm population and the quality of regional perinatal-neonatal healthcare system may be helpful to re-evaluate and optimize the standard of care and health insurance policy in the transitional period of China [6,13].

Methods

Study population, protocol and ethical approval

The concept and protocol of investigation, definition of diagnosis of preterm morbidity and mortality as well as specific disease severity and level of care were adopted from the references cited in the manuscript, during the data collection, analysis and preparation of manuscript in 2018-2020. This study followed the whole regional birth population survey in 2015, in which a complete birth data was prospectively collected from totally 107 level I-III hospitals providing obstetric care (6 municipal, 16 county and 85 township), and 8 level II and 4 level III hospitals equipped with neonatal wards and/or intensive care units (NICU) [11,20]. Non-medical abortions (especially unplanned pregnancy) were

excluded. The above birth data was integrated with the data on all hospitalized preterm infants derived from the complete birth population in whole region, retrospectively retrieved from regional perinatal information database (Fig. 1). The study protocol was approved by the ethic committee of Children's Hospital of Fudan University, and accepted by HWCH as well as all participating hospitals in Huai'an [11,20]. As no specific intervention was applied, informed consent from parents/guardians was waived. Preterm birth was defined as delivery at 25⁺⁰-36⁺⁶ weeks of GA, divided into extreme (EPT, 25⁺⁰-27⁺⁶ weeks), very (VPT, 28⁺⁰-31⁺⁶ weeks), moderate (MPT, 32⁺⁰-33⁺⁶ weeks) and late (LPT, 34⁺⁰-36⁺⁶ weeks) preterm groups [21,22]. Those of EPT below 25 weeks of GA were not included due to very few numbers and parental decision not to provide resuscitation at delivery. Incidences of EPT, VPT, MPT, LPT and total preterm births were presented as per thousand (‰) of the number of total births (including term and post-term births) of whole region.

Definitions of preterm morbidity and mortality

The diagnostic criteria of pregnancy, perinatal and neonatal co-morbidities and complications are presented in additional file 1 [23-34]. Definitions regarding vital statistics are based on the original survey [11,20], and the 10th revision of the international classification of diseases [35]. Briefly, GA was mainly determined by the date of last menstrual period and/or fetal sonography in early pregnancy, or postnatal assessment by new Ballard score when prenatal records were missing or incomplete [36]. Birth weight (BW) was measured at birth. Small for GA was defined as a BW < 10th percentile for gender and GA [37]. Birth defects (BD) were identified prenatally or within the first seven postnatal days (PND) [11,20]. Severity of neonatal underlying diseases were characterized as requiring intensive or critical care based on the treatment strength during hospitalization, such as degree of the disease severity, in need of non-invasive/ mechanical ventilation (NIV/MV), surfactant, vasopressor, or surgery, etc (also see additional file 1) [7,28,38]. Fetal death was deemed to be synonymous with stillbirth. Deaths at delivery room (DR) referred to those born alive but died during resuscitation, usually after parents' requests for withdrawal or withholding [39]. Perinatal mortality included stillbirths and neonatal deaths within first seven PND. Neonatal mortality was defined as deaths of livebirths within 28 PND, including deaths at DR. All-death was defined by including stillbirths, neonatal deaths or, for EPT and VPT, within 44 weeks of adjusted post menstrual age. In-hospital death was defined as deaths during hospitalization or, for EPT and VPT, within 44 weeks of adjusted post menstrual age. For those hospitalized in NICU but had early withdrawal at parental request, the outcome was estimated by attending physicians based on discharge or follow-up record.

In birth population, incidences of perinatal and neonatal morbidities were presented as percentage (%) with the number of preterm total births and livebirths excluding deaths at DR as denominator, respectively. In hospitalized population, incidences of postnatal morbidities were presented as percentage (%) with the number of total preterm admissions as the denominator. Rates (%) of perinatal mortality, stillbirths, deaths at DR and all-death were divided by the number of total preterm births. Neonatal mortality rates (%) were divided by the number of preterm livebirths (including deaths at DR) [20]. In-hospital death rates (%) were divided by the number of preterm livebirths excluding deaths at DR in birth

population, or the number of total preterm admissions in hospitalized population, respectively. The GA-specific mortality rates (% where numerators and denominators were both limited within specific GA stratum) [7,40] were adopted and corrected by the number of total births or livebirths of whole region [41], and presented as per 1,000 (‰, for calculation see Table 2).

Representativeness of HWCH and risk factors of deaths

To estimate the representativeness of HWCH of whole region, whole regional preterm births and hospitalized preterm infants were divided into HWCH and non-HWCH groups, respectively. Furthermore, the HWCH admissions were divided into inborn and out-born to compare the efficacy of perinatal-neonatal care by hospital categories (Fig. 1). Risks of all-death for preterm births and in-hospital death for preterm admissions were analyzed to determine the role of HWCH in the whole region, taking the effects of perinatal interventions and the underlying neonatal morbidities into consideration.

Statistical analysis

EPIDATA database was used for datasheet recordings and subjected to SPSS software (V. 16.0, SPSS Inc. Chicago, IL) for statistical analysis. Continuous variables were presented as mean and standard deviation (SD) or median [interquartile ranges]. One-way analysis of variance or non-parametric Mann-Whitney test was used for comparison among groups. Categorical variables were presented as number and rate, using a two-tailed Pearson Chi-squared or Fisher's exact test where appropriate. $P < 0.05$ was considered statistically significant. Death risks of preterm births and hospitalizations were analyzed by uni- and multi-variable (binary) logistic regressions. Values measuring relative risks were given as odds ratio (OR) with 95% confidence intervals (CI).

Results

Preterm morbidity and mortality of whole region

Of the 59,245 regional total births (and 59,056 livebirths), 2,651 (4.5%) were preterm, with preterm perinatal and neonatal mortality rates being 8.4% and 4.3%, respectively (Table 1). The incidences of EPT, VPT, MPT, LPT and total preterm of the total births of whole region were 1.4, 5.3, 7.2, 30.8, and 44.7‰, and all-death rates were 1.0, 1.6, 0.6, 1.1 and 4.3‰, respectively (Table 2). The GA-specific all-death rates of 25, 26, 27 and 28 weeks were 100, 78.1, 56.4 and 52.1%, and in-hospital death rates 100, 70.0, 48.3 and 30.4%, with a 50% survival rate achieved by 28 and 27 week of GA, respectively.

Of 2,487 preterm livebirths excluding deaths at DR, the hospitalization and in-hospital death rate was 78.0% and 3.5%, respectively (Table 1). In 1,941 hospitalized preterm infants, 35.2% and 23.1% received intensive and critical care (Table 3), with in-hospital death rates being 0.6% (4/684) and 18.5% (83/449), respectively. The top five morbidities in hospitalized preterm infants were hyperbilirubinemia (59.0%), pneumonia/sepsis (40.0%), RDS (14.1%), IVH (11.0%) and hypoglycemia (10.8%). Surfactant and NIV/MV were applied in 11.2% and 39.9% hospitalized preterm infants, respectively (Table 3).

Representativeness of HWCH

In the 59,245 total births of whole region, 9,405 (15.9%) were born in HWCH, with significantly higher rates of major pregnancy complications and preterm birth (> three-fold) than those of non-HWCH hospitals (Table 1). Of the whole region, proportions of births and all-deaths for EPT in HWCH were 71.8% and 78.7%, respectively. A total of 1,025 (52.8% of whole region) preterm infants were hospitalized in HWCH (802 inborn and 223 out-born). The in-hospital death rate was significantly higher in out-born than inborn infants, especially within 7 PND, and in VPT and LPT (Table 3). Compared to non-HWCH, the rate of hospitalized preterm infants received critical care was four-time higher in HWCH, with significantly longer length of stay, higher costs, and higher rates of in-hospital deaths and major morbidities (Table 3).

Uni- and multi-variable logistic regression analysis

In general, for the variables with moderate to high relative risks of deaths by univariable regression analysis, it tended to become mild or no risk by multivariable regression analysis. Significant all-death risks were found for the total preterm births in BW < 1,000g, II-III degree of amniotic fluid contamination, Apgar-5 min \leq 7, and BD (Table 4A). For the hospitalized preterm infants, significant in-hospital death risks were found in out-born of HWCH, GA < 32 weeks, Apgar-5 min \leq 7, BD, RDS, necrotizing enterocolitis and NIV/MV (Table 4B), whereas born in HWCH, ANG, cesarean delivery and surfactant use were protective factors against death (Table 4A and B).

Declarations

Our study demonstrated the incidences of perinatal and neonatal morbidity and mortality rate by GA strata of total preterm births or hospitalized preterm infants, from a complete birth population in an emerging region of China. So far, data on perinatal and neonatal outcome in China are more based on multi-center hospital admission-based investigations, with a lack of perinatal data from the regional birth-population perspective [42-45]. As a result, our understanding on the incidence of preterm birth, morbidity and mortality in China is significantly biased, making it difficult to compare at the national and international level. We assumed that Huai'an region represents the national average level of economic status and healthcare. It may reflect the actual perinatal-neonatal healthcare style and quality in at least one-fourth of sub-provincial prefectural regions in China. Our data showed approximately 4.5% of preterm birth rate and 10% preterm mortality rate. This may be translated into annually 650,000 preterm births and 65,000 deaths in China. The concept, methodology and data file of the current study may be generalized to other regions or provinces, and served as a benchmark for future large-scale studies to explore perinatal-neonatal healthcare and quality improvement, especially in terms of EPT management.

The incidence of EPT (25-27 weeks of GA, 1.4‰ of total births, Table 2) was first reported from birth population-based survey data from China, and was markedly lower than those (3-5‰ of total births) in developed countries [3-9]. Despite the benefits provided by the universal health insurance policy for hospitalization and delivery, especially for families with lower socioeconomic status, it remains controversial whether active prenatal and peripartum management including aggressive resuscitation at

delivery, and neonatal critical care should be provided to EPT in emerging regions in China. As deaths in livebirths below 28-week GA may be registered as abortion or stillbirth [19], or as neonatal death only after 7th of PND (unpublished recommendation for birth registry since 2018), it can cause potential bias on vital statistics of the incidence and outcome of preterm births and mortality [7,17,18], leading to inaccurate estimation of the quality improvement of perinatal-neonatal care.

The comparison of preterm outcome between HWCH and non-HWCH admissions shed light on the role of main transferal centers in regional perinatal-neonatal network. As revealed in Table 1 and 3, HWCH treated a disproportionately large part of high-risk pregnancies in the Huai'an region [20], and admitted more extremely and very preterm infants requiring critical care than other regional institutions. This supports a central role of HWCH in the regional perinatal-neonatal healthcare, and indicates that investigation of the leading centers may help to understand the perinatal-neonatal healthcare at the regional level. Of note, the vast sub-provincial prefectural regions in China are estimated to account for more than 80% of annual national births (of > 15 millions). The inter-institutional difference in infrastructure should be narrowed with recent socioeconomic development, but quality of maternal-neonatal healthcare remains to vary widely. By including all birth data from level I-III institutions in the whole region of Huai'an [11,20], our study has overcome the limitations encountered in previous reports of vital statistics which often failed to account for EPT [6,17-19]. Based on earlier nationwide collaborative studies, the quality of perinatal-neonatal healthcare at HWCH is likely to be above the national average level [11,20,42,43] and may be referred to for future inter-regional comparisons.

There was a trend that those with high or moderate risk of death by univariable regression analysis tended to have mild or no risk by multivariable logistic regression model (Table 4), well denoting that with decent obstetric management for high risk pregnancy and delivery, as well as NICU service quality, death risks of preterm birth and hospitalization may be effectively mitigated. As estimated by relative death risks of preterm birth and hospitalization through multivariable regression model, these should have explained, at least in part, the discrepancy of GA-specific mortality rates between birth and hospitalized population [7-11]. We therefore speculate that it should enable a comprehensive assessment of quality improvement in the regional perinatal-neonatal healthcare infrastructure as well as survival quality in follow-up of very and extremely preterm infants [1-5,8,9].

The main limitation of the study was a relatively small sample size of EPT and VPT. However, as the first report of outcome of all hospitalized preterm infants derived from the total regional birth population, this study, on the other hand, has accounted for a large number of perinatal and postnatal risk factors. Another limitation of the study was that no details of peripartum intervention were included for the perinatal risk analysis. Nevertheless, information on preterm morbidity and mortality by GA and efficacy of perinatal interventions may represent to a large part the regional perinatal-neonatal outcome given the proportion of preterm infants requiring critical care and out-born infants transferred to HWCH.

Conclusion

In conclusion, these preterm birth- and hospitalization-based morbidity and mortality by GA strata or hospital categories, reflect the healthcare quality of regional network. Regional transferal center, such as HWCH, may to a large part represent the perinatal-neonatal healthcare in emerging regions. The concept and protocol of regional birth population-based surveys have been validated by our current study, and should be extended to other regions across China to gain comprehensive understanding in the world-wide campaign for prevention of preterm birth.

Abbreviations

ANG, antenatal glucocorticoids; BD, birth defects; BPD, bronchopulmonary dysplasia; BW, birth weight; DR, delivery room; EPT, extreme preterm; GA, gestational age; HWCH, Huai'an Women and Children's Hospital; IVH, intraventricular hemorrhage; LPT, late preterm; MPT, moderate preterm; MV, mechanical ventilation; NICU, neonatal intensive care unit; NIV, non-invasive ventilation; PND, postnatal day(s); RDS, respiratory distress syndrome; VPT, very preterm.

Declarations

- Ethics approval and consent to participate

The ethics committee of Children's Hospital of Fudan University approved the study design and protocol, and waived the need for consent (#2019-194). This approval was adopted and approved by Huai'an Women and Children's Hospital and all participated hospitals in accordance with the Chinese regulations for clinical practice and investigation (www.nhc.gov.cn). The permissions and the names of the ethics committees and scientific committees (institutional review board) of the major participating hospitals are referred to Zhu X, et al. *BMC Pregnancy Childbirth*. 2019; 19(1): 224.

- **Consent for publish:** Not applicable.

-Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

- Competing interests

All the authors have declared no any financial and non-financial competing interests to disclose.

- Fundings

Supported by grants from the Project of Maternal and Child Health Care by Jiangsu Provincial Commission of Health (F201402 [Yue H]), the National Natural Science Foundation (No. 81501288 [Dong Y]) and Shanghai Municipal Commission of Health (Project Young Physician Investigator [Dong Y]). The

funding body had no influence on the design of the study, collection, analysis, and interpretation of data, and in writing the manuscript.

- Authors' contributions

Xiaojing Guo executed the study protocol, data collection and analysis, drafted and revised manuscript.

Xiaoqiong Li and Zhaojun Pan supervised and validated clinical data collection and analysis, and reviewed manuscript.

Tingting Qi, Xiaoqin Zhu and Hui Wang carried out data collection and analysis, and reviewed manuscript.

Ying Dong engaged in data analysis, and critically revised manuscript.

Hongni Yue conceptualized and designed the study, coordinated and supervised data collection and analysis, and critically revised manuscript.

Bo Sun conceptualized and designed the study, supervised data analysis, and critically revised manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for respective aspects of the work.

-Acknowledgements

The authors thank all the committed staffs from member hospitals, as well as those at township hospitals and health care services, of the Huai'an Perinatal-Neonatal Study Group for generous participation and support of the study. Contribution of Drs. Y. Xu, MD and S. Luo, MD from Children's Hospital of Fudan University in data collection is highly appreciated.

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Tables

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Figures

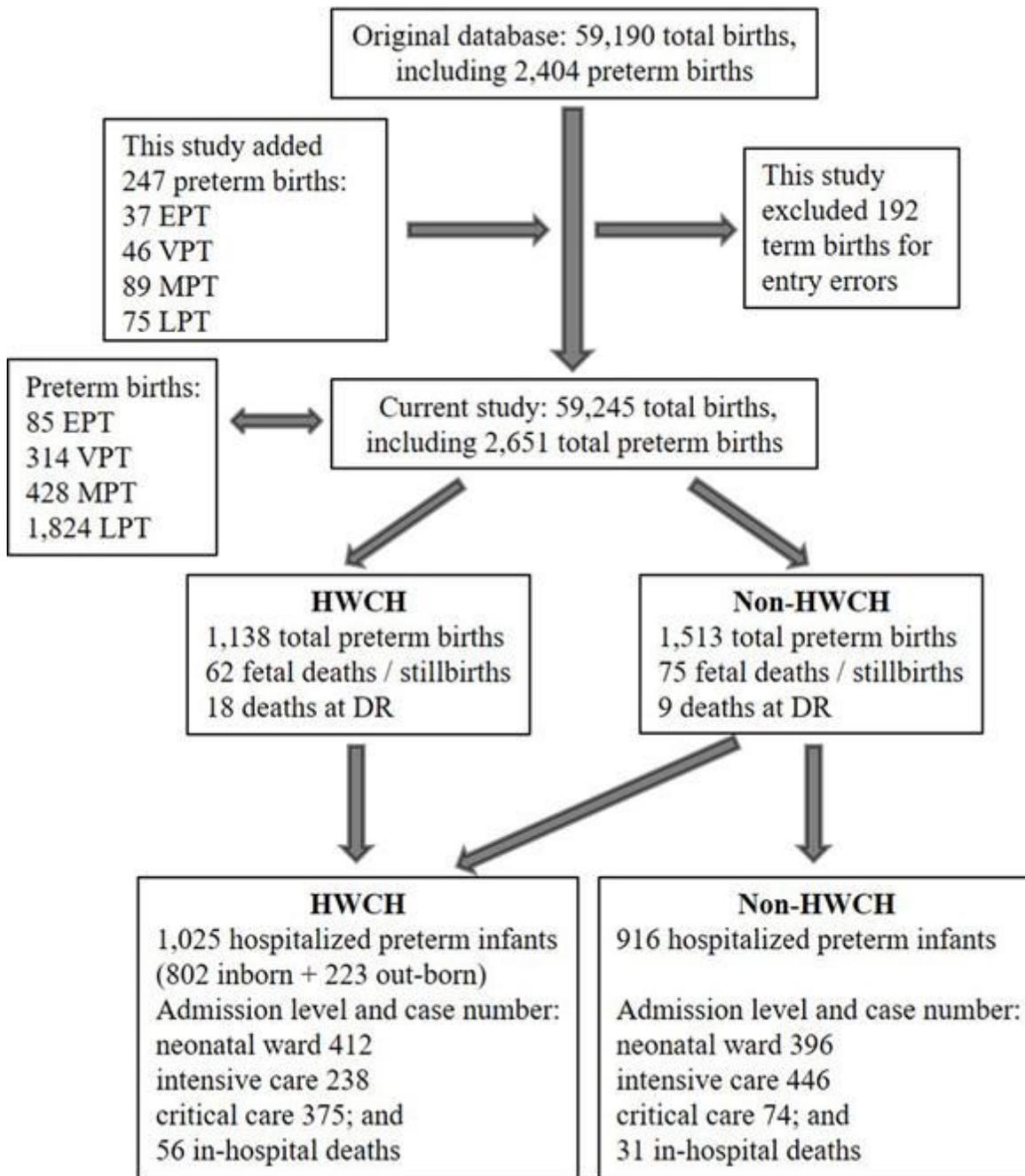


Figure 1

The flowchart of database and enrolled preterm population by gestational age strata and hospital categories. Abbreviations: EPT, extremely preterm; VPT, very preterm; MPT, moderate preterm; LPT, late preterm; ET, early term. For definitions of deaths and other abbreviations see Table 1 legends.

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