

Severe Neurodevelopmental Impairment in Neonates Born Preterm: Impact of Varying Definitions in a Canadian Cohort

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Objective To assess the impact of variations in the definition of severe neurodevelopmental impairment (NDI) on the incidence of severe NDI and the association with risk factors using the Canadian Neonatal Follow-Up Network cohort.

Study design Literature review of severe NDI definitions and application of these definitions were performed in this database cohort study. Infants born at 23-28 completed weeks of gestation between 2009 and 2011 (n = 2187) admitted to a Canadian Neonatal Network neonatal intensive care unit and assessed at 21 months' corrected age were included. The incidence of severe NDI, aORs, and 95% CIs were calculated to express the relationship between risk factors and severe NDI using the definitions with the highest and the lowest incidence rates of severe NDI.

Results The incidence of severe NDI ranged from 3.5% to 14.9% (highest vs lowest rate ratio 4.29; 95% CI 3.37-5.47). The associations between risk factors and severe NDI varied depending on the definition used. Maternal ethnicity, employment status, antenatal corticosteroid treatment, and gestational age were not associated consistently with severe NDI. Although maternal substance use, sex, score of neonatal acute physiology >20, late-onset sepsis, bronchopulmonary dysplasia, and brain injury were consistently associated with severe NDI irrespective of definition, the strength of the associations varied.

Conclusions The definition of severe NDI significantly influences the incidence and the associations between risk factors and severe NDI. A standardized definition would facilitate site comparisons and scientific communication. (*J Pediatr* 2017;■■■:■■■-■■■).

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Infants born very preterm have a greater risk of long-term adverse neurodevelopmental outcomes compared with infants born at term,¹ with consequential impacts on the life of the child, the family, the healthcare system, and society. Many publications report the incidence of neurodevelopmental impairments (NDIs) in cohorts born very preterm at diverse ages using different definitions. Severe NDI typically is reported as a composite outcome that includes some or all of the following domains: cerebral palsy, cerebral palsy severity, motor, cognitive, language, and hearing and visual impairments. Except cerebral palsy, these outcomes exist on a spectrum, can be measured using various assessment tools, and often change as the child matures. There is no consensus on the definition of severe NDI, and the impact of variations of the definition is unknown.

The Canadian Neonatal Follow-Up Network (CNFUN) national outcome data include cerebral palsy and severity as measured via the Gross Motor Function Classification System (GMFCS), as well as motor, cognitive, and language scores from the Bayley Scales of Infant and Toddler Development, Third edition (Bayley-III)

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BSID-II	Bayley Scales of Infant Development, Second Edition
CNFUN	Canadian Neonatal Follow-Up Network
CNN	Canadian Neonatal Network
GMFCS	Gross Motor Function Classification System
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
SNAP-II	Score for Neonatal Acute Physiology, Second Edition

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Portions of this study were presented as an abstract at the Canadian National Perinatal Research Meeting, February 10-13, 2016, Banff, Alberta, Canada; the Pediatric Academic Societies Annual Meeting, April 30-May 3, 2016, Baltimore, Maryland; and the Society for Pediatric and Perinatal Epidemiologic Research 29th Annual Meeting, June 20-21, 2016, Miami, Florida.

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in addition to vision and hearing assessment at 18-21 months' corrected age for infants born very preterm at <29 weeks of gestation. The CNFUN network recently reported the incidence and determinants of severe NDI,² and this report underscored the controversy related to definitions of severe NDI and the challenges in comparing rates of severe NDI in the published literature.

The goal of this study was to evaluate current definitions of severe NDI used to categorize children born very preterm at 18-30 months of corrected age. We aimed to quantify the effect of varying definitions on incidence rates of severe NDI and to assess how these definitions affect the associations between severe NDI and risk factors by applying the various definitions to the CNFUN dataset.

Methods

A literature and internet search was used to identify current definitions of severe NDI. Neonatal or neonatal follow-up networks that include post-neonatal intensive care unit (NICU) discharge outcomes were identified with the key words "neonatal network" and "neonatal follow-up" in a Google search, as well as individual entry or combinations of the terms "neonatal," "premature," "prematurity," "preterm," "disability," "impairment," and "follow-up" in a PubMed search. The literature search was limited to studies or reports published in the past 10 years to target current definitions of severe NDI, and well-defined inclusion criteria were applied (Table I; available at www.jpeds.com). For individual components of severe NDI including Bayley-III motor, language, and cognitive scores, we were interested in the definition expressed as SD from the normative mean.

The study population included infants born at 23-28 weeks of gestation between April 1, 2009, and September 30, 2011, and admitted to a NICU participating in the Maternal Infant Care study who were evaluated in the CNFUN network at a targeted age of 18-21 months of corrected age. The Canadian Institutes of Health Research Team in the Maternal Infant Care study linked Canadian Neonatal Network (CNN) data from 28 participating sites with CNFUN data from all 26 Canadian Neonatal Follow-Up Networks and captured approximately 90% of Canadian NICU admissions during this time period.² In this study, infants who were stillborn, moribund, with major congenital anomalies, or admitted to NICU >24 hours after birth were excluded. Recruitment and follow-up of infants born very preterm in this cohort have been described previously.² To summarize in brief, detailed information (eg, gestational age, birth weight, pregnancy complications, delivery data, maternal and infant characteristics, and neonatal morbidity) on infants admitted to 28 participating NICUs in the CNN was abstracted by trained personnel using a manual of definitions. Health, sensory, and neurodevelopmental status were evaluated via the use of standard protocols developed by CNFUN. Ethics approval was obtained at all sites for the Canadian Institutes of Health Research Team in the Maternal Infant Care study, and specific institutional review board approval for this study was obtained from the Children's and

Women's Research Ethics Board at the University of British Columbia (H15-00605) and the Executive Committee of the CNFUN.

The incidence rates of severe NDI using the definitions identified in the literature review were calculated for the CNFUN cohort. Rate ratios and 95% CIs were calculated to compare differences in the rates, using the definition with the lowest incidence rate as a reference (Table II). Rates of each individual component of severe NDI also were calculated (Table III).

Potential risk factors for severe NDI were identified from the literature¹¹⁻²⁵ and included (1) sociodemographic and risk factors occurring during pregnancy (ethnicity, caregiver/maternal education and employment status, smoking, illicit substance use, parity, multiple gestation, premature rupture of membranes for >24 hours); (2) risk factors at birth, such as 5-minute Apgar score, gestational age, sex, outborn status (not born at a CNN NICU site); and (3) neonatal risk factors, such as Score for Neonatal Acute Physiology, Second Edition (SNAP-II), brain injury defined as either intraventricular hemorrhage grade 3 or greater or persistent periventricular echogenicity, retinopathy of prematurity grade 3 or greater, bronchopulmonary dysplasia (defined as requirement of respiratory or oxygen support at 36 weeks' corrected postmenstrual age or at the time of transfer to Level 2 units), and sepsis (positive culture in blood or cerebrospinal fluid in a symptomatic neonate after 2 days of age). Definitions from CNN²⁶ and CNFUN² were used.

In bivariate analysis, potential risk factors identified from the literature^{2,11-25} were examined for their association with both (1) the least stringent severe NDI definition with the highest incidence vs (2) the most stringent severe NDI definition with lowest incidence rate (Table IV). χ^2 or Fisher exact tests were used to assess statistical significance of the association for categorical variables, and the *t* test or Wilcoxon rank-sum test was used for continuous variables ($P < .05$). These analyses were considered exploratory and were performed to determine which variables to include in the multivariable regression analysis.

Two sets of logistic regression analyses were used to examine independent associations between risk factors and severe NDI; the first set included the least stringent severe NDI definition and the second set of models included the most stringent definition. Each set of analyses consisted of 4 logistic regression models and included risk factors identified as significant in the respective bivariable analysis; in the first stage, the regression model included only sociodemographic and pregnancy characteristics, the second stage included significant factors from the previous model and perinatal risk factors, and the third stage model included significant factors from the previous model and neonatal risk factors. The final models for each severe NDI definition included only risk factors significantly associated with the respective outcome ($P < .05$).

To compare aORs for both final models, all factors significantly associated with either severe NDI definition in the final regression models were used in the extended regression models (one with the least stringent severe NDI definition and one with most stringent definition). Thus, all factors significantly

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