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REVIEW ARTICLE

# Neurodevelopmental outcomes after neonatal surgery

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**Abstract**
Children who require surgery in the newborn period are at risk for long-term neurodevelopmental impairment (NDI). There is growing evidence that surgery during this critical window of neurodevelopment gives rise to an increased risk of brain injury, predisposing to neurodevelopmental challenges including motor delays, learning disabilities, executive function impairments, and behavioral disorders. These impairments can have a significant impact on the quality of life of these children and their families. This review explores the current literature surrounding the effect of neonatal surgery on neurodevelopment, as well as the spectrum of proposed mechanisms that may impact neurodevelopmental outcomes. The goal is to identify modifiable risk factors and patients who may benefit from close neurodevelopmental follow-up and early referral to therapy.

**Keywords** Neurodevelopment · Infants · Surgery · Anesthesia · Inflammation · Analgesia

## Introduction

The survival of infants who require surgery in the neonatal period has increased in the last few decades due to significant advancements in pediatric surgery and in perioperative care [1]. With improvement in neonatal surgical mortality, attention has shifted, in part, to mitigating postoperative neonatal morbidities, including brain injury and subsequent neurodevelopmental impairment (NDI). However, follow-up studies on the neurodevelopmental outcomes in this cohort of children show significantly greater NDI in motor and cognitive scores compared with age-matched controls in the general population [2, 3].

The majority of studies that have assessed neurodevelopmental outcomes after neonatal surgery have focused on cardiac surgery, while the studies of outcomes after noncardiac neonatal surgery have been limited [2, 3]. As such, this review will focus largely on outcomes after noncardiac neonatal surgery, with neurodevelopmental outcomes after neonatal cardiac surgery summarized elsewhere [4–6].

There are several converging factors that may place children at risk for NDI after neonatal noncardiac surgery. Early exposure to anesthesia is thought to predispose a rapidly developing, vulnerable brain to injury by altering the process of synapse formation (synaptogenesis) [7] and by impairing cerebral autoregulation [3]. Similarly, the trauma of surgery is thought to lead to brain injury by inducing a systemic inflammatory response that can disrupt the blood brain barrier and promote infiltration of immune cells into the brain [8]. Additionally, inadequate postoperative pain management and persistent activation of pain receptors (nociceptors) in the developing brain can lead to early brain injury [7, 9, 10]. These mechanisms are currently under study as potential modifiable risk factors of poor neurodevelopmental outcomes in children who have undergone noncardiac neonatal surgery.

This review aims to summarize the literature regarding neurodevelopmental outcomes of infants who require surgery and explore the possible pathophysiologic mechanisms underlying these outcomes. Early recognition of NDI in this susceptible cohort of children facilitates early referral and prevention of long-term of morbidity.

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## Epidemiology of surgery in the neonatal period

The World Health Organization (WHO) estimates that 6% of newborns worldwide are born with a congenital anomaly [11]. Approximately 240,000 newborns worldwide die within the first month of life from such anomalies [12]. In the United States (US), the most common cause of infant mortality is due to birth defects, accounting for 20% of all infant deaths [13]. Congenital heart defects (CHD) are the most common birth defect, affecting approximately 40,000 neonates per year and nearly 1% of all infants born in the United States [14]. Many of these cardiac defects will require surgical repair at some point during the patient's lifetime [15]. Across 96 North American centers, cardiac surgery during the neonatal period account for 25% of 80,000 CHD surgeries between 2007 and 2010 [15]. Although the mortality of infants born with CHD remains high, the 1-year survival rate has been improving due to advancements in medical and surgical interventions [16]. Between 1999 and 2017, the mortality of infants less than 1 year of age from CHD decreased from 45.14 to 29.52% in the United States [17]. The decline in mortality is likely multifactorial, in part driven by improvements in antenatal diagnosis, early postnatal detection, advancement in surgical techniques, and multidisciplinary care in the postoperative period [18].

After CHD, gastroschisis (GS) and congenital diaphragmatic hernia (CDH) are two of the most common congenital anomalies that require surgery in newborns [19]. Gastroschisis occurred in 1 in 50,000 births between 1974 and 2003 across four continents [20], while CDH occurred in 2.8 per 10,000 births between 1974 and 2015 across 19 countries [21]. Across 16 Canadian centers, more than half (52%) of gastroschisis repairs were performed within 6 h of neonatal intensive care unit (NICU) admission, and the success rate was 81% among the 1400 cases in which surgery was performed [19]. When comparing neonatal complications after gastroschisis repair between 2005 to 2011 and 2012 to 2018, there was a decrease in NEC (6 versus 3%), abdominal compartment syndrome (2 versus 1%), wound infection (11 versus 9%), total parental nutrition (TPN) on discharge (14 versus 5%), and cholestasis (22 versus 9%) [19]. The overall survival rate to discharge was 97.3% [19]. The mortality is similar between Canada and the US for complex gastroschisis at 10.8 and 9.3%, respectively, while there is a significant difference in mortality from simplex gastroschisis 1.4 and 3.4% in Canada and US, respectively [22].

Of the 808 complete live births of neonates with CDH in 16 Canadian centers, the overall survival rate is 80.2% [19]. When comparing neonatal complications after CDH repair between 2005 to 2011 and 2012 to 2018, there was a decrease in necrotizing enterocolitis (NEC) (3 versus 0.8%), wound infection (4.0% versus 2.6%), TPN on discharge (5.0 versus 3.6%), CDH recurrence (1.9% versus 1.8%), tube feeding (26 versus 25%), CNS injury as defined by antiepileptic use at discharge (3 versus 2%), oxygen at discharge (23 versus 6%), and cholestatic liver disease (12 versus 2%) [19]. The CDH survival at 5 years of age was similar between North America and Europe, which ranged from 64.6 to 75.8% and 63.9 to 76.6%, respectively [21]. There is a statistically significant decrease in overall CDH mortality rate between 2001 and 2012, with a—2.43% in average annual percentage change [21].

While gastroschisis and CDH affect late preterm and term infants at a median gestational age of 35.8 and 38 weeks, respectively [19], preterm infants are at an increased risk of requiring surgery due to necrotizing enterocolitis (NEC). NEC is a devastating gastrointestinal disease that predominately affects preterm infants. Between 1993 and 2013, the incidence of NEC ranged from 7 to 13% of preterm infants born annually between gestational age of 22 to 28 weeks and weighing between 401 and 1500 g across 26 academic centers in the US [23]. In another US epidemiological study that extracted data from hospital discharge records, NEC-associated hospitalization occurred in 110 per 100 000 livebirths with an in-hospital mortality rate of 15.2% [24]. NEC is associated with significant morbidity, where many of these diagnosed infants will require surgical interventions and prolonged hospitalizations. In 2000, 27.2% of infants diagnosed with NEC had at least one surgical intervention and an overall median hospitalization of 49 days [24].

In summary, the morbidity and mortality of infants who require surgical interventions in early childhood are improving due to advancements in surgical and postoperative management. Given that a larger proportion of children are surviving serious neonatal illness, we must now identify opportunities to improve the long-term neurodevelopmental outcomes in these patients.

## Neonatal cardiac surgery and neurodevelopment

CHD is the most common reason for neonatal surgery and can serve as a paradigm for understanding the risks of brain injury. Similar to neonates who have undergone noncardiac surgery, neonates who had cardiac surgery have more long-term neurodevelopmental challenges compared to the general population [2, 6, 9, 25]. Commonly identified NDI include gross and fine motor delays, learning disabilities, and language difficulties [26]. Numerous studies that have followed children after neonatal cardiac surgery at different time points reported similar results of NDI in the cardiac

surgery group compared to their controls [25, 27]. Gunn et al. completed a follow-up study of infants who had cardiac surgery for CHD by 2 months of age and found, at 2 years, that they had statistically lower mean motor, language, and cognitive scores as compared to the normative data, based on assessment with Bayley Scales of Infant Development (BSID)-III [25]. Similarly, significant delays were seen in motor, language, and cognition on BSID-III at 1 year of age in a group of infants who had cardiac surgery before 3 months of age compared to their control group [27].

Multiple factors have been identified to increase the risk of NDI in patients who had neonatal cardiac surgery. Not surprisingly, patient-specific risk factors include a concurrent genetic syndrome and the type of cardiac lesion. CHD occurs in at least 15% of those diagnosed with a genetic syndrome [14], such as Trisomy 21, Noonan's syndrome, Williams syndrome, and DiGeorge syndrome [5]. Gaynor et al. assessed over 1700 children who had cardiac surgery between 1996 and 2009 and found that children who had cardiac surgery had lower Psychomotor Development Index (PDI) and Motor Development Index (MDI) scores on the BSID-II assessment at 14.5 months of age compared to their controls [6]. The presence of an underlying genetic anomaly was associated with lower MDI and PDI on the BSID-II [6]. The type of cardiac lesion can also modify neurodevelopmental outcomes. Gunn et al. found that term infants who had cardiac repair surgery for single ventricle pathology performed the worst on the BSID-III at follow-up at 2 years of age compared to other forms of CHD [25]. Possible mechanisms include underlying hemodynamic and neuronal metabolic ratio abnormalities associated with these single ventricle cardiac pathologies, which increase the risk of severe neurologic insults in these patients compared to other forms of CHD [28].

Other patient-specific risk factors associated with neurodevelopmental delays include lower gestational age and smaller head circumference [25]. Term infants with complex CHD, such as hypoplastic left heart syndrome (HLHS) and transposition of great arteries (TGA), who had preoperative brain MRI showed a delay of 1 month in brain maturation compared to their healthy controls [29]. Delay in brain development may be explained by the innate circulatory abnormalities and compromised fetal cerebral blood flow, as measured by low cerebral-to-placental resistance (CPR) ratio ($< 1$) in neonates with CHD [30]. Consistent with findings that patients with single ventricle pathology having worse neurodevelopmental outcomes [25], infants with single ventricle pathologies have lower CPR ratio compared to other forms of CHD [30]. A low CPR is an indication of the fetus attempting to decrease cerebral vascular resistance to maintain blood flow to the brain at the expense of other organs in a relatively hypoxic environment [30]. Despite this attempt at cerebral autoregulation, these infants have smaller head circumferences, highlighting inadequate blood flow to maintain normal brain development [30]. These studies suggest that circulatory compromise leads to a smaller head circumference and delays in brain maturation, thereby increasing the risk of NDI.

Circulatory arrest and cardiopulmonary bypass (CPB) are two operative risk factors that increase the risk of NDI. Bellinger et al. compared two groups of infants who underwent arterial switch operation for transposition of the great arteries (TGA), where one group underwent deep hypothermic total circulatory arrest, while the other group had deep hypothermic low-flow CPB [31]. In comparison to the CPB group, the circulatory arrest group scored lower in PDI on BSID and had increased neurological complications, most commonly hypertonia, hypotonia, and cerebral palsy at 1-year follow-up [31]. Not surprisingly, the longer the duration of circulatory arrest, the lower the PDI score [31]. There was no significant association on MDI scores between the two groups, but the circulatory arrest group performed worse compared to the CPB group [31]. To look at the effect of CPB duration on neurocognitive outcomes, Sterling et al. compared children who had cardiac surgery at less than 18 years requiring long CPB and short CPB times [32]. The median age of repair ranged from 1 to 5.6 years across the four groups [32]. Additionally, the authors compared children who had atrial septal defect (ASD) surgical repairs (short CPB time) with percutaneous repairs (no CPB time) [32]. The duration of CPB was based on the complexity of the CHD on the Aristotle Complexity Basic Score, with a higher score indicating a more complex lesion [32]. The authors defined long CPB time as repairs of complex lesions (Aristotle score of 2 or greater), short CPB time as shunt repairs (Aristotle score of 1), and no CPB time as percutaneous closures [32]. The neurocognitive risk in the complex group (longer CPB duration) was 19.5% higher than in the shunt group (shorter CPB duration) [32]. The risks of NDI was greater when the age of repair occurred before the age of 10 [32]. There was no significant difference in neurocognitive outcomes in the atrial septal defect repair group with short CPB duration compared to the percutaneous closure with no CPB time [32]. Although the precise timing of CPB was not reported in this study, the outcome suggests that longer duration of hypoxia is associated with poorer outcomes. Similarly, Hicks et al. found that aortic cross clamp time greater 70 min in children who had arterial switch operation for TGA scored lower in language development on the BSID-III at follow-up at 2 years of age [33].

Postoperative factors that have been identified to increase the risk of NDI at 2 years of age in infants who had cardiac surgery less than 2 months of age include biochemical signs of acidosis immediately and 24 h after surgery, as well as prolonged hospital stays [25]. The association between acidosis and NDI likely reflects compromised end-organ

perfusion in the immediate postoperative period. The pH level post-surgery had a significant association with language development at 2 years of age [25]. Similarly, the lactate level at 24 h after surgery had a significant association with cognitive delay at 2 years of age [25]. Higher lactate levels on admission and on day 1 post-surgery and longer duration of elevated lactate were predictors of mortality and poorer neurodevelopmental outcome at 18 months in a group of children who had cardiac surgery before the age of 6 weeks [34]. Read et al. evaluated the neurodevelopmental outcomes of children who had cardiac surgery at less than 1 year of age at 2–3 years with BSID-III and found that children with multiple morbidities and the need for extracorporeal life support had an increased risk of cognitive and language delays compared to children with no morbidities [4]. They also found that longer hospitalizations are associated with poorer outcomes, although prolonged hospital stays may be a surrogate for a more complicated hospital course [4].

Brain injury sustained during neonatal cardiac surgery from poor cerebral perfusion may also be associated with neuropsychiatric disorders including attention deficit/hyperactivity syndrome (ADHD) [35]. Czobar et al. compared the severity of ADHD in children who had their first cardiac surgery before and after 3 years of age [36]. The authors found that children who had cardiac surgery after 3 years of age had more severe ADHD symptoms 10 years after cardiac surgery compared to children who had their first surgery before 3 years of age and the control group [36]. Neuroplasticity, the ability for the brain to remodel and adapt to injury in the younger age group, was identified by the authors as a protective factor from more severe illness when the cardiac repair had occurred earlier in life [36].

## Neurodevelopmental outcomes after neonatal noncardiac surgery

The majority of the literature on neurodevelopmental outcomes of infants after surgery focuses on those who underwent cardiac surgery, and there is comparatively limited literature on neurodevelopmental outcomes after noncardiac surgery. There is growing concern that infants who had noncardiac surgery are similarly at risk of NDI [2]. With the increase in the survival of these children after noncardiac surgery, it is important to refocus our attention on identifying the risk factors that contribute to their neurodevelopmental morbidity long-term.

In a meta-analysis of neurodevelopmental outcomes at 12 and 24 months after neonatal noncardiac surgery, Stolwijk et al. found that these children had lower motor and cognitive scores at 0.6 standard deviations (SD) and 0.5 SD below the population average, respectively, on the BSID-II–III [3]. One of the limitations of this meta-analysis is the high degree of heterogeneity in the types of noncardiac surgeries that were included [3]. When patients were subdivided into groups of CDH, abdominal wall defects, and esophageal atresia surgery, patients in the CDH group scored 1 SD below the population average, while those in the abdominal wall defects repair group scored 0.5 SD below the population [3]. However, no difference was identified between in the esophageal atresia repair group and to the general population [3]. Multiple risk factors for NDI were identified, including prematurity, low birth weight, additional congenital anomalies, multiple surgeries, and prolonged hospital stay [3].

## Neuroimaging in infants who require neonatal surgery

Neuroimaging provides insight into brain injury and abnormal neurodevelopment in children who undergo neonatal surgery, and neuroimaging may be a means to risk-stratify infants at risk for NDI. Beca et al. evaluated brain magnetic resonance imaging (MRI) of 153 infants with a mean gestational age of 38.8 weeks, who had cardiac surgery with and without cardiopulmonary bypass for CHD at less than 8 weeks of age preoperatively, 1 week postoperatively, and 3 months postoperatively [37]. Preoperative brain injury was seen in 26% of these infants, and white matter brain injury was found in 20% of these infants. At 1-week postoperatively, 42% of these infants developed new white matter injury on MRI, while none developed new brain injury on MRI at 3 months postoperatively [37]. There was a significant association between brain immaturity and white matter injury on preoperative MRI [37]. Lower brain maturity score may be due to the underlying circulatory abnormalities associated with CHD, leading to the inability to maintain adequate cerebral blood flow in-utero for normal brain development [30]. However, neurodevelopmental follow-up of the survivors and assessment with the BSID-III at 2 years of age showed no association between white matter injury and neurodevelopmental outcomes [37]. One of the limitations of this study is that the majority of survivors had mild white matter injury, and therefore, follow-up at 2 years of age may not have been long enough to identify milder forms of NDI [37]. However, infants who had more immature brains on the 3-month postoperative MRI had lower motor, language, and cognitive scores on the BSID-III [37].

Similarly, Stolwijk et al. found evidence of brain injury after noncardiac neonatal surgery when preoperative brain ultrasounds were compared to postoperative brain MRIs at 7 days in 101 preterm and term infants [38]. There was a heterogeneity of noncardiac surgeries included in the study, including intestinal atresia, esophageal atresia, and

anorectal malformation repairs [38]. Parenchymal and non-parenchymal injuries after noncardiac surgery appear to be more common in preterm infants (74%) compared to term infants (58%) [38]. Similarly, brain injury was identified on brain MRI performed 4 weeks post-surgery or by discharge in neonates who had surgery for CDH, esophageal atresia, and abdominal wall defects, compared to their age- and sex-matched controls [39]. The authors found that infants who had surgery had higher risk of white matter abnormalities and delays in brain maturation in comparison to the control group [39].

## Exposure to anesthesia and neurodevelopmental outcomes

Most our understanding on neurotoxic effects of anesthesia come from pre-clinical animal studies. In rodents, exposure to anesthetic agents leads to apoptosis (programmed cell death) in the developing brain and abnormal synaptogenesis [40–42]. It is difficult to predict the period of neurotoxic vulnerability in humans by extrapolating data from rodent studies, as the timing of synaptogenesis is vastly different between rodents and humans [43]. In trying to identify the relative period of brain neurotoxic vulnerability, Ing et al. studied the initial age of anesthetic exposure and neurodevelopmental outcomes in human children at 10-year follow-up [44]. They found that an initial exposure under the age of 3 years increased the risk of language and cognitive disabilities, while these risks are not seen when anesthetic exposure occurred after the age of 3 years [44]. However, initial exposure after 3 and up to 5 years of age is associated with motor impairments [43].

Surgery is also a time of potential hemodynamic instability and the developing brain may be particularly sensitive to changes in neurovascular tone given the immaturity of cerebral autoregulation [38]. The immaturity in cerebral autoregulation can be further exacerbated while under anesthesia for term infants and even more so in premature infants [38]. Exposure to anesthesia during the neonatal period may result in brain injury and subsequent poor neurodevelopmental outcomes secondary to these fluctuations in cerebral perfusion [38].

Nestor et al. explored the question of whether longer duration or higher frequency of anesthetic exposure are associated with NDI. The authors determined that the duration of general anesthesia (up to and greater than 181 min) does not have an effect on neurodevelopmental outcomes [40]. However, similar to other studies, multiple independent exposures to general anesthesia were identified as a risk factor for poor neurodevelopmental outcomes [40, 41, 45, 46]. The neurotoxic effects of anesthesia seem to accumulate with increasing episodes of anesthetic exposure, with a 35% risk of learning disability with repeated anesthesia compared to 20% risk with a single exposure for children who were exposed to general anesthesia before the age of 4 [46]. On the contrary, a single exposure to anesthesia was associated with a similar neurodevelopmental outcome as compared with patients who were naive to any anesthesia [46]. Sprung et al. found similar results when they compared babies born to mothers under general anesthesia versus regional anesthesia. They found no association in learning disability between these two groups, highlighting that a single, short exposure to anesthesia does not affect long-term neurodevelopmental outcomes [47].

Birajdar et al. have shown similar results on the neurodevelopmental outcomes after a single exposure to anesthesia of infants postnatally compared to the general population [48]. Infants anesthetized by sevoflurane for isolated intestinal malrotation correction surgery had similar one-year developmental outcomes compared to the population norm in mean general quotient [48]. No children in this study developed cerebral palsy, sensorineural deafness or blindness [48]. The General Anesthesia Study (GAS) trial, an international and multicenter randomized control trial (RCT), corroborated these findings [49]. In the GAS trial, the authors compared the neurodevelopmental outcome at 5 years of age in babies who underwent inguinal herniorrhaphies either under general anesthesia or awake-regional anesthesia during infancy [49]. There was no significant difference in the neurodevelopmental outcomes between the awake-regional group compared to the general anesthesia group [49], again showing that a single exposure to anesthesia in infancy is not associated with NDI. However, the single exposure to anesthesia had a median time of 54 min [49] and we may not be able to extrapolate this to other surgical interventions that extend beyond an hour of general anesthesia.

Beyond childhood neurodevelopmental disorders, Håkanson et al. explored whether exposure to anesthesia is associated with subsequent social and neuropsychiatric disability in adulthood. In that study, children who had neonatal abdominal surgery were followed up at a median age of 28 years to determine whether exposure to anesthesia is associated with disadvantaged social outcomes, such as in education, employment, and ADHD [50]. Infants who had abdominal surgery at a median age of 7 days and at a median gestational age of 38 weeks were compared with their age- and sex-matched controls. The authors found no statistical significance in educational level, income, and ADHD prevalence between the two groups in adulthood [50].

The association between exposures to anesthesia on NDI remains an active area of research, as some parents may choose to delay surgical procedures beyond infancy to protect the developing brain from exposure to anesthesia and injury. However, many surgical interventions during

the neonatal period are lifesaving and unavoidable. Further research should seek to identify best practices in perioperative care that provide optimal neuroprotection. Studies with follow-up beyond 5 years of age may be informative to understand risk of school-age neurocognitive or social impairments.

## Inflammation during surgery

The brain and the immune system communicate extensively during development. Immune cells and secreted immune-related molecules, such as cytokines, are important drivers of neurodevelopment. Microglia, the resident macrophages in the central nervous system (CNS), not only play an important role in active immune defense in the brain, but they also mediate neuronal development by responding to environmental signals in the CNS [51]. Neuro-immune interactions contribute to neurogenesis (birth of new neurons), neural migration, and synapse formation, refinement, and elimination, among other processes.

A multitude of intrauterine and early life stressors, including malnutrition, infection, metabolic imbalance, and drug exposure, can disrupt the trajectory of early neurodevelopment, thereby predisposing offspring to profound, lifelong consequences for cognition and psychiatric disease risk. Surgical intervention is one of these stressors that trigger systemic inflammatory responses leading to release of proinflammatory molecules, recruitment and activation of immune cells, endothelial dysfunction, tissue injury, and organ damage [52]. During this proinflammatory state, alterations in neural connectivity, synaptogenesis, and myelination can disrupt normal brain development and increase the vulnerability of these infants to brain injury and NDI [7, 51, 53].

Change in circulating cytokines has been studied as one biomarker for inflammation during and after surgery. Pavcnik-Arnol et al. measured the serum concentration of select cytokines before surgery and immediately and up to 2 days postoperatively in neonates who underwent surgical interventions for gastroschisis, small intestinal atresia, CDH, esophageal atresia, coarctation of the aorta, or other neurosurgical interventions [54]. Not surprisingly, interleukin-6 (IL-6), and interleukin-8 (IL-8) were shown to be elevated significantly from baseline when measured postoperatively, indicating that surgery is associated with a surge in cytokines leading to systemic inflammation [54].

During cytokine storm, the proinflammatory markers that are released have the potential to affect the rapidly developing brain and increase susceptibility to NDI. Dion Nist et al. conducted a literature review on the temporal trajectory of cytokine alteration to determine the cytokines most predictive of poor neurodevelopmental outcomes in preterm babies [55]. The authors found that IL-6, IL-8, TNF-a, and IL-1B are most consistently predictive of poorer neurodevelopmental outcomes, especially when they are measured within the first three weeks of life [55]. From day 20 of life and onwards, higher level of IL-8 was most consistently associated with poor outcomes [55]. One study found that higher levels of IL-6 measured 3 h after cardiopulmonary bypass in cardiac surgery was most predictive of poorer motor outcome, but was not associated with cognition in children older than 3 months and younger than 7 years [56]. The neurological assessments were conducted pre-surgically and at 6 months post-surgically [56].

While there are limited studies on the effect of cytokine surge after surgery on neurodevelopmental outcomes, we may be able to extrapolate from the more widely studied association between NEC and NDI. In a study that measured cytokines in preterm infants with median age of 28 weeks at the time they were diagnosed with Bell's stage II and III NEC, the authors found the level of IL-6 was significantly elevated in the NEC group compared to their controls [57]. Neurodevelopmental assessments of these infants at 24–28 months found that infants in the NEC group had lower MDI and PDI scores on the BSID-II [57], although abnormal neurodevelopment outcomes were not consistently correlated with the level of IL-6, IL-8, and TNF-a [57]. Similarly, in a meta-analysis that compared the neurodevelopmental outcomes of preterm infants with medically versus surgically treated NEC, the authors found that the infants with NEC had lower cognitive and motor scores at 20 months of age [58]. Patients who had surgical intervention for NEC for Bell's stage III diagnosis had 2.3 times higher risk of NDI compared to the medically treated NEC group [58]. Furthermore, there was no significant difference between the medically treated NEC group and control group in NDI [58].

It is likely that the interaction between various cytokines cause a cumulative systemic inflammatory response, thereby affecting brain development. Cytokines are not only elevated in the setting of surgery. Preterm delivery, maternal chorioamnionitis, and severe neonatal illness may induce a systemic inflammatory response [55]. Regardless of the source of inflammation, cytokine release has been shown to be associated with NDI [59], especially if exposure occurs in the first three weeks of life [55]. Further studies are needed to look at the neurotoxic implications of these cytokines in vivo and to identify the cytokines most consistently associated with NDI. Whether these cytokines are causative or correlative remains to be fully understood.

## Implications of postoperative pain and analgesia on neurodevelopment

Recognition and management of neonatal pain has improved significantly in recent decades. Up until the 1980s, anesthesia during painful procedures was underutilized for neonates due to concerns of potential adverse effects and the incorrect assumption that neonates are incapable of feeling pain [60]. Since then, growing evidence demonstrates that neonates have the anatomical and functional capabilities, including the neural, hormonal and metabolic pathways and the behavioral and physiological abilities, to mount a response to nociceptive stimuli and the ability to sense pain [61, 62]. One study showed that infants experience noxious stimuli starting as early as 25 weeks of gestation when cortical activity was measured with near-infrared spectroscopy (NIRS) and the ability to sense pain intensifies with increasing postmenstrual age [63]. Neonates routinely undergo painful and invasive procedures while in the NICU as part of their routine care, and surgery only exacerbates the noxious stimuli they experience.

Persistent activation of nociceptors in human neonates can have damaging effects on their vulnerable, developing central nervous system leading to poor long-term neurodevelopmental outcomes [7, 9, 10, 64]. Grunau et al. found a correlation between the increased number of skin-breaking procedures with lower cognitive and motor outcomes in preterm infants at 8- and 18-months corrected age [65]. The association is independent of illness severity and exposure to opioid and dexamethasone [65]. The alterations to pain response in these preterm neonates seem to persist into adulthood with increase in pain sensitivity [10]. Similarly, Schneider et al. found that premature infants who were exposed to more invasive procedures had significantly smaller brain volumes and slower growth of the thalami and basal ganglia on brain MRI at term gestation and poorer neurodevelopmental outcomes on the BSID-II at 18 months of age [64]. Oral glucose during painful procedures did not mitigate these effects, as higher exposure to glucose was similarly associated with poorer brain neuroimaging results and neurodevelopmental outcomes [64].

Most of our understanding of neonatal pain came from studies of neonatal rat pups who were exposed to repetitive painful stimuli to mimic the preterm neonates' experience in the neonatal intensive care unit (NICU) [66–68]. Repetitive painful experiences alter the neonatal rat pups' pain threshold and increase their vulnerability to stressful stimuli in adulthood [66–68]. Anand et al. divided neonatal rat pups into two groups, noxious and control, where they were either stimulated on the heel with a needle or cotton swab, respectively, between one, two, to four times per day for 7 days to mimic the blood sampling process by heel pricking in human neonates [66]. Anand found that rat pups who were in the noxious group and who received stimuli four times a day had a statistical significance in lower pain thresholds with quicker withdrawal from the hot plate test compared to their controls [66]. Rat pups who were exposed to noxious stimuli similarly had increased anxiety and alcohol preference compared to their controls [66]. Similarly, Duhresen saw brain morphological changes with higher apoptotic scores in rat pups who were injected with formalin to induce pain compared to those who received saline or no injections, especially if the injections were given earlier in life (between day 1and 5 versus day 10 and 12) [67]. These studies with rat pups suggest that pain exposures in early life can have detrimental behavioral and brain morphological effects.

Opioids are commonly used for pain and sedation in neonatal intensive care units [69, 70]. In neonatal rat pups, pre-treatment with morphine is protective against neural apoptosis in the context of repetitive painful stimuli [67]. On the other hand, the NeoPain trial, a morphine analgesic study in human children, showed that pre-treatment with morphine did not reduce neurological morbidities [70]. In the NeoPain trial, ventilated preterm infants were pre-emptively treated with morphine infusions as an analgesia to protect them from developing intraventricular hemorrhage (IVH) and periventricular leukomalacia [70]. The trial found that morphine infusion treated clinical pain, but there was no statistical significance between the morphine group versus the placebo group in neurological outcomes [70].

Excessive opioid usage is not without its own consequences. In the NeoPain trial, the morphine group developed hypotension more frequently compared to the placebo group, and infants who had more open-label morphine boluses developed poorer outcomes [70]. Prolonged use of opioids and benzodiazepines have also been shown to increase neonatal morbidities in preterm infants, such as necrotizing enterocolitis and bronchopulmonary dysplasia, as well as lower BSID-III scores in motor, cognition, and language, at 2 years of age [71]. Infants who are exposed for a short period of time (< 7 days) seem to have higher scores on the BSID-III and better outcomes compared with those exposed for longer durations [71]. Further research is needed to determine the optimal duration of analgesia treatment and whether pre-treatment for routine painful procedures is beneficial.

## Conclusion

Substantial progress has been made in the survival of neonates who require surgery in early life. Studies on the neurodevelopmental outcomes of these children after cardiac

and noncardiac surgery show that they are at significant risk of long-term NDI. Proposed mechanisms include disruptions in early brain development from exposure to anesthesia, postoperative systemic inflammation, and inadequate pain control. Future research efforts should focus on opportunities to modify these and other identified risk factors to reduce NDI risk in this vulnerable population.

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**Data Availability** No primary data produced as part of this study, and therefore no data available to access.

## Declarations

**Competing interests** The authors declare no competing interests.

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