Title: “Association Between Maternal Hypertension and Infant Neurodevelopmental Outcomes in Extremely Preterm Infants”

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1. ABSTRACT:

Background: Maternal hypertension is associated with prematurity and its complications in neonates, but it is unclear whether preterm infants exposed to maternal hypertension experience poorer neurodevelopmental outcomes compared to infants born prematurely without exposure to maternal hypertension. Therefore, we aimed to assess the association between exposure to maternal hypertension and neurodevelopmental impairment (NDI) at 24 months of age, compared with no such exposure in a cohort of extremely premature infants born <29 weeks.

Method: We conducted a retrospective observational cohort study using data from two neonatal units in Montreal, Canada. We included infants born at 23+0 to 28+6 weeks from 2011 to 2017 who were admitted within the first 24 hours of life and who attended their 24-month corrected age follow-up appointment for a neurodevelopmental assessment. The exposure of interest was infants' exposure to maternal hypertension during pregnancy with/without being small for gestational age (SGA). We assessed our outcomes using the Bayley Scales of Infant and Toddler Development - third edition (Bayley-III). Our primary outcome was the presence of any NDI, and the secondary outcome was the presence of significant NDI. Using multiple logistic regression analysis, results were adjusted for potential confounders (maternal diabetes, gestational age at birth category (<26 weeks vs. ≥26 weeks), as well as cesarean delivery or prolonged premature rupture of membranes >24 hours [PROM]) as these factors are known to be associated with both maternal hypertension and an adverse infant neurodevelopmental profile.

Results: Of 1019 preterm infants, we included 647 infants: 96 (15%) were exposed to maternal hypertension, 71 (11%) were exposed to maternal hypertension and had an SGA status, 551 (85%) were unexposed to maternal hypertension and 523 (81%) were unexposed to maternal hypertension or were not SGA. Infants exposed to maternal hypertension were born to older

mothers, more frequently by cesarian delivery and less frequently with PROM and maternal diabetes. Also, on average, those infants were born at a later estimated gestational age, more often SGA and singleton. In the group exposed to maternal hypertension with concomitant SGA status, there were more cesarian section delivery, less PROM and maternal diabetes. Infants exposed to maternal hypertension had higher rates of any NDI (n=55/96 (57%) vs. n=252/551 (46%)) and significant NDI (n=21/96 (22%) vs n=86/551 (16%)). Accordingly, maternal hypertension was associated with any NDI (crude OR: 1.64; 95%CI=1.06-2.55 and adjusted OR: 2.26; 95%CI=1.39-3.72), and significant NDI (crude OR: 1.51; 95%CI=0.87-2.55) and adjusted OR: 1.89; 95%CI=1.02-3.41) at 24 months. Maternal hypertension with SGA was associated with any NDI (crude OR: 3.23; 95%CI=1.38-8.42 and adjusted OR: 4.49; 95%CI=1.77-12.96) and significant NDI (crude OR: 3.80; 95%CI=1.60-8.69 and adjusted OR: 4.77; 95%CI=1.76-12.33). After stratification by gestational age category (<26 weeks and ≥26 weeks), infants exposed to maternal hypertension born ≥ 26 weeks (traditionally less at risk of NDI) still showed significantly higher odds of any NDI (1.9; 95% CI= [1.18-3.09]).

Conclusion: Maternal hypertension was associated with a higher risk of adverse neurodevelopmental outcomes in extremely preterm infants. These findings outline the need for better control of maternal hypertension to improve the trajectory of premature offspring, offering early intervention to maximize their neurodevelopmental potential.

2. RÉSUMÉ:

Contexte: L'hypertension maternelle est associée à la prématurité et à ses complications chez les nouveau-nés, mais il n'est pas clair si les nourrissons prématurés exposés à l'hypertension maternelle présentent davantage de déficit neurodéveloppemental comparé à celui des nourrissons nés prématurément sans exposition à l'hypertension maternelle. Par conséquent, le but de notre étude est d'explorer le lien entre l'exposition à l'hypertension maternelle et la présence d'un déficit neurodéveloppementale (DND) à l'âge de 24 mois corrigé, chez une cohorte de nourrissons de moins de 29 semaines.

Méthode: Notre étude est observationelle et rétrospective. La cohorte analysée a été créée à partir de données provenant de deux unités néonatales à Montréal, au Canada. Nous avons inclus les nourrissons nés entre 23+0 et 28+6 semaines, de 2011 à 2017, qui ont été admis dans les 24 premières heures après leur naissance et qui ont évalué lors de leur rendez-vous de suivi à 24 mois corrigé dans le contexte d'une évaluation neurodéveloppementale. L'exposition à l'étude était la présence d'hypertension maternelle durant la gestation, avec ou sans présence d'un petit poids pour l'âge gestationnel (PAG). Notre issue primaire était la présence d'un DND, quelqu'en soit la sévérité, et l'issue secondaire était la présence d'un DND significatif. En utilisant une régression logistique multivariée, les analyses ont été ajustées afin de tenir compte de facteurs confondants potentiels, tel que le diabète maternel, une naissance à l'extrême de la prématurité (<26 semaines ou ≥26 semaines), ainsi qu'un accouchement par césarienne ou une rupture prématurée des membranes prolongée de plus de 24 heures). En effet, ces facteurs sont associés à la fois à l'hypertension maternelle et à des atteintes neurodéveloppementales chez les nourrissons.

Résultats: Sur 1019 bébés prématurés admis durant la période à l'étude, nous avons inclus 647 nourrissons : 96 (15 %) exposés à l'hypertension maternelle, 71 (11 %) exposés à l'hypertension

maternelle et né PAG, 551 (85 %) non exposés à l'hypertension maternelle et 523 (81 %) non exposés à l'hypertension maternelle et non PAG. Les nourrissons exposés à l'hypertension maternelle sont nés de mères plus âgées plus fréquemment par accouchement par césarienne et moins fréquemment exposés à une rupture prolongée et au diabète maternel. En moyenne, ces nourrissons sont nés à un âge gestationnel plus avancés, plus souvent PAG et plus souvent de grossesse unique. Dans le groupe exposé à l'hypertension maternelle avec le statut concomitant de PAG, il y avait davantage de césarienne, moins de rupture prématurée prolongée des membranes et moins de diabète maternel. Les nourrissons exposés à l'hypertension maternelle présentaient des taux plus élevés de DND (n=55/96 (57 %) par rapport à n=252/551 (46 %)) et de DND significatif (n=21/96 (22 %) par rapport à n=86/551 (16 %)). Par conséquent, l'hypertension maternelle était associée à la présence d'un DND (RC non-ajusté : 1.64; intervalle de confiance [IC] à 95 % = 1.06-2.55 et RC ajusté : 2.26; IC à 95 % = 1.39-3.72), et à un DND significatif (RC non-ajusté : 1.51; IC à 95 % = 0,87-2,55) et à un RC ajusté : 1.89; IC à 95 % = 1.02-3.41) à 24 mois corrigés. L'hypertension maternelle associée à l'PAG était associée à un DND (RC non-ajusté : 3.23; IC à 95 % = 1.38-8.42 et RC ajusté : 4.49; IC à 95 % = 1.77-12.96) et à un DND significatif (RC non-ajusté : 3.80; IC à 95 % = 1.60-8.69 et RC ajusté : 4.77; IC à 95 % = 1.76-12.33). Après la stratification par catégorie d'âge gestationnelle à la naissance (<26 semaines et ≥26 semaines), les nourrissons exposés à l'hypertension maternelle nés à ≥26 semaines (traditionnellement moins à risque d'atteinte neurodéveloppementale) présentaient tout de même une probabilité significativement élevée de DND (1.90; IC à 95 % = [1.18-3.09]).

Conclusion: L'exposition à un était hypertension durant la grossesse est associée à un risque accru d'atteinte neurodéveloppementale chez le nouveau-né extrêmement prématuré né à <29 semaines de gestation. Nos résultats soulignent la nécessité d'évaleur si une amélioration du contrôle de

l'hypertension maternelle peut se traduire en une amélioration de la trajectoire neurodéveloppementale de l'enfant dans un contexte de grande prématurité. Ainsi, l'exposition à hypertension maternelle est un facteur de risque permettant d'identifier les grands prématurés nécessitant une intervention précoce afin de maximiser leur potentiel neurodéveloppemental.

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5. PREFACE & CONTRIBUTIONS OF AUTHORS:

This thesis was written following the manuscript-based thesis guidelines. I am the first author that presents the substantive contribution of my work. I performed the literature review, the methods and design, analyzed and interpreted the data, and wrote the manuscript. I also prepared for the submission to a peer-reviewed journal. I am targeting the "Pediatrics" journal.

Drs. Dayan and Altit helped with the study design, statistical analyses, interpretation of data, and critical revision and editing of the thesis and manuscript for important intellectual content. Dr. Brown helped develop and interpret the results and critically reviewed the study. Drs. Beltempo, Lapointe, Gorgos, and Mai Luu gave critical revisions to the manuscript. All authors will approve the final manuscript before submission to a journal and will agree to be accountable for all aspects of the work before final publication in the scientific literature.

6. LIST OF ABBREVIATIONS:

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)

Bronchopulmonary dysplasia (BPD),

Cerebral palsy (CP)

Confidence interval (CI)

Gross Motor Function Classification System (GMFCS)

Hypertensive disorders of pregnancy (HDP)

Intraventricular hemorrhage (IVH)

Necrotizing enterocolitis (NEC)

Neonatal Intensive Care Unit (NICU)

Neurodevelopmental impairment (NDI)

Odds ratio (OR)

Periventricular leukomalacia (PVL)

Premature rupture of membranes (PROM)

Retinopathy of prematurity (ROP)

Small for gestational age (SGA)

The score for Neonatal Acute Physiology-II (SNAP-II)

World Health Organization (WHO)

7. INTRODUCTION:

Prematurity rates have increased in developed countries over the past 20 years, affecting about 10 % of all births worldwide.[1-3] In the United States, preterm birth has accounted for up to 75% of neonatal mortality and 50% of morbidities such as neurodevelopmental impairment (NDI), especially cerebral palsy (CP) and intraventricular hemorrhage (IVH).[4] Infants born <29 weeks' gestation are at significant risk of CP, other NDI and behavioural disabilities.[5]

Several maternal factors, including stress, smoking, intrauterine infection, as well as chronic and acute diseases, contribute to preterm birth and growth restriction.[6] Globally, up to a fifth of preterm births are due to hypertension during pregnancy.[7] In-utero exposure to a maternal hypertensive environment has been associated with altered infant growth and brain development.[8-10] However, less is known about how maternal hypertension impacts childhood neurodevelopment after preterm birth.[11]

Regardless of exposure to maternal hypertension, preterm infants have an increased risk for long-term neurodevelopmental adverse outcomes compared to those born full-term.[12-14] Indeed, 25% of extremely preterm infants have some significant NDI, commonly identified between 18 and 24 months of age, including CP.[15] The incidence of CP among children born < 29 weeks is 4% and 0.1% in children born at term.[5,16,17] Whether exposure to maternal hypertension is linked with child NDI independent of prematurity is unclear. Hence, to address these knowledge gaps, we sought to assess the association between exposure to maternal hypertension and the risk of NDI at 24 months of age among extremely preterm infants. We hypothesized that maternal hypertension is associated with poorer neurodevelopmental outcomes after accounting for gestational age at birth and other factors.

8. BACKGROUND AND RATIONALE:

8.1. Prematurity:

8.1.1. Epidemiology and global burden of prematurity:

The World Health Organization defines preterm birth as giving birth before 37 completed weeks of gestation, very preterm birth between 29 and 32 weeks of gestation and extremely preterm birth at less than 29 weeks.[18-21] In 2014, about 11% of live births, accounting for about 15 million births, were born preterm worldwide, corresponding to 1 in 10 live births, and about 7% (one million) of these infants died in the first month of life.[19,20] Globally, more than 25% of neonatal deaths, represented by more than 1 million infant deaths, are attributed to preterm birth.[3] Preterm birth rates have remarkably increased in developed countries over the past 20 years, reaching around 10 % of all births. [1-3] In 2014, over 500,000 preterm births were born in Europe and North America, with 11.4 % of all deliveries occurring preterm.[22] More than 25,000 premature infants are born annually in Canada.[23]

In Canada in 2016, the preterm birth rate was around 8%, and after excluding delivery room deaths, the survival rates among neonatal intensive care unit (NICU) admissions in 2020 of 22, 23, 24, 25, and 26 weeks' gestation were 27, 49, 73, 85 and 89 % respectively.[24,25] In the United States, preterm birth is the foremost cause of infant mortality, representing around 75% of birth mortality and more than 50% of neonatal morbidities.[4] Approximately 1% of live births in the United States were born at less than 28 weeks of gestation in 2013.[18] Preterm infant with intrauterine growth restriction is at a higher risk of neonatal mortality and morbidities compared to infants born with an appropriate growth for gestational age.[26]

8.1.2. Risk factors for preterm birth:

Several factors have been implicated in increasing the risk of preterm birth, such as socio-demographic, psychological, nutritional, socioeconomic, and environmental factors.[6,27] A large systematic review of forty-five studies assessed the association between ethnicity and preterm delivery and found a 2-fold increase in the odds of preterm birth for those of black ethnicity (OR 2.0, 95% CI 1.8-2.2); however, Asian, Hispanic, or Caucasian women showed no significant associations.[28] Interestingly, two meta-analyses have stated that air pollution is associated with increased preterm delivery.[29,30] Also, maternal emotional stress during pregnancy, such as disruptive life events and partner violence, is associated with increased odds of preterm birth (OR: 1.42; 95% CI= 1.21-1.63).[31-33] Also, Low maternal education and socioeconomic status have also been associated with preterm delivery.[34]

Maternal factors (i.e. stress, smoking, alcohol use, intrauterine infection, and acute and chronic diseases such as maternal hypertension) and fetal factors are responsible for 30 to 35% of preterm births, while spontaneous preterm labour and preterm premature rupture of membranes account for the remaining 65-70%.[6] Globally, up to a fifth of preterm births are due to maternal hypertension.[7] Many other maternal conditions during pregnancy have been shown to increase the risk of preterm delivery, including diabetes, anemia, obesity, short stature, polycystic ovarian syndrome, uterine anatomy (e.g., short cervical length less than 25 mm, bicornuate uterus and large intrauterine fibroids) and placental conditions (e.g., abruptio placentae and placenta previa).[35] On the other hand, fetal conditions such as congenital anomalies are 5-fold more likely among preterm infants vs. full-term infants, representing about 15% of the preterm birth.[36] Although advanced maternal age (>40 years) appears to have a high risk of preterm delivery; a meta-analysis reported

that nulliparous females <18 years had the highest odds of preterm delivery among all women (OR: 1.52; 95% CI= 1.40-1.66).[37]

8.1.3. Protective factors in prematurity:

The National Institute of Child Health and Development Neonatal Research Network reported that increased adherence to care practices, such as perinatal care, antenatal steroids, prenatal antibiotics, cesarian delivery, surfactant therapy, and adoption of evidence-based oxygen saturation targets, improve neonatal outcomes. These practices and care bundles are associated with a significant rise in survival rates without major neonatal morbidities, such as decreased rates of retinopathy of prematurity (ROP) and lung injury.[38] In Canada, reports from the Canadian Neonatal Network have described that improved perinatal and neonatal care resulted in significant improvements in survival among extremely preterm newborns.[39] A cutting-edge Cochrane review, including ten trials (about 4730 women and 5650 babies), assessed the effectiveness and safety of repeated doses of prenatal corticosteroids and reported a reduced risk of infant respiratory distress syndrome (risk ratio [RR] 0.83; 95%[CI]=0.75- 0.91) and serious infant outcomes (including CP and developmental delay; RR: 0.84; 95% CI=0.75-0.94).[40] Also, the Canadian Preterm Birth Network, a non-profit organization of families, supports the use of early steroid administration prenatally for mothers with a high risk of premature birth.[23]

8.1.4. Short-term complications of prematurity:

Despite remarkable advances in perinatal and neonatal care, complications of prematurity remain a major concern. Worldwide in 2016, complications of prematurity were the leading cause of death in children under five years, representing 35% of deaths among newborns.[20] In Canada, about 10% of live births are preterm, and up to 35% of children born at less than 29 weeks gestation are re-hospitalized during the first two years of life.[39] In 2014, Johnston *et al.* estimated that the

annual cost to the healthcare system associated with preterm birth in Canada was up to $587.1 million.[41]

Prematurity complications are divided into short-term (neonatal) and long-term complications. The overall risk of complications is inversely proportional to gestational age, while survival rates are directly proportional to gestational age.[18] In a prospective multicenter study, Rysavy *et al.* found that among the survivors in a cohort of about 5000 newborns, the rate of severe disability was 33, 24, 19, and 14% in those born at 22, 23, 24, and 25 weeks gestation, respectively.[42] Extreme prematurity (being born at <29 weeks) is associated with the highest incidence of morbidity in all infants ages, including bronchopulmonary dysplasia (BPD), late-onset sepsis, necrotizing enterocolitis (NEC), IVH, and ROP.[25] An English cohort study of 3378 extremely premature newborns born between 22 and 26 weeks reported that over 80% of these infants were admitted to the NICU, and 10% of them died after delivery.[18,43] In the same cohort, among the 1041 infants alive at discharge, almost 60% had significant complications of their prematurity, including BPD, ROP, NEC, and abnormal brain on cranial ultrasound.[18,43] Many morbidities, including IVH, have been linked to deliveries following preterm labour and premature rupture of membrane >24 hours (PROM). A neonatal neurosonographic study performed on 745 preterm infants reported abnormal scans, including IVH and periventricular leukomalacia, in almost 39% of infants born after a preterm delivery and in 33% of those born following a PROM.[44]

Many scoring systems can measure the severity of illness after birth, such as the Score for Neonatal Acute Physiology-II (SNAP-II). This index is intended to assess the illness severity and predict the risk of mortality, morbidity and prognosis at admission to the neonatal intensive care unit. A high SNAP-II score (≥38) may be associated with severe adverse short-term outcomes (death).[45] The severity of illness and its complications can increase the risk for long-term disability.

8.1.5. Long-term complications of prematurity:

The morbidity of prematurity is not constrained to the neonatal period but extends later in life. Even though the clinical care of preterm infants has improved, a more significant number survive with NDI resulting in long-term disability.[38] These lifelong morbidities include CP, deafness, blindness, language impairment, learning disability and cognitive delay.[46]

8.1.5.1. *Cognitive and language impairment:*

Cognitive delay is the lag in obtaining and understanding knowledge acquired through thoughts, senses, and experiences.[47] Many factors play a role in increasing the risk of NDI in preterm infants, such as neonatal septicemia, BPD, NEC, IVH grades 3 and 4.[46] Pierrat *et al*. screened more than 5500 preterm infants at 24 months of age and reported that the risk of developmental and cognitive delay was 50% for infants born at 24–26 weeks and 41% for infants born at 27–31 weeks.[16] Using the Bayley Scales of Infant and Toddler Development - third edition (Bayley-III), Pascal *et al.* reported that the cognitive delay for preterm infants, followed from 18 months until six years of age, had a pooled prevalence of 16.9% (95%CI: 10.4–26.3%). The risk of delay in survivors declined with increased gestational age (the risk of delay at 23, 24, 25 and 26 weeks of gestation was 51%, 34%, 27%, and 16%, respectively).[48] A prospective Swedish study of 456 extremely preterm infants, also using the Bayley-III performed at a median age of 30.5 months, reported that the preterm group had a higher risk of severe cognitive delay compared to term infants (6.3% vs. 0.3%).[17]

The BOOST-II trials were two parallel studies conducted in the United Kingdom and Australia to assess the safest ranges of oxygen saturation in preterm infants born before 28 weeks. The investigators evaluated the cognitive and language disability outcomes using the Bayley-III composite scores. They defined “significant” and “any” impairment as Bayley-III composite

scores of <70 and <85, respectively.[49] Furthermore, in the United States, a study on 4987 infants born at 24 hospitals with significant (severe) cognitive impairment (defined as a Bayley-III composite cognitive score <70) showed that the rate of severe cognitive impairment among surviving preterm infants was 9.3%.[42]

8.1.5.2. *Motor impairment and cerebral palsy:*

CP is a set of disorders permanently affecting the development of posture and movement, causing motor restrictions.[50] It is a non-progressive condition that occurs during an infant's brain development.[50] CP has a broad range of severity and includes various types of impairment, which occurs in almost 0.2% of live births.[50] It is often classified according to the pattern of the affected limbs. In monoplegia, only one limb is affected. In hemiplegia, just a longitudinal half of the body is involved. In extensive cases, both arms or legs (diplegia) or all four extremities (quadriplegia) are involved.[51]

One of the most common classification systems for CP is the Gross Motor Function Classification System (GMFCS), which provides a severity level for CP [52]. Indeed, the GMFCS is a 5-level classification system that scores children's self-initiated gross motor function [52]. The infant with CP is objectively categorized depending on the severity of the lower limb impairment, emphasizing sitting, walking, and wheeled mobility. The score scale is from 1 to 5. An increasing score represents a rising severity of the motor impairment(s). Differences between the five levels are centred on functional abilities, quality of movement and the need for assistive technology, including walkers, crutches, canes, or wheeled mobility. For infants two years of age and less, the distinctions between levels I and II are less noticeable than for other levels.[52,53]

In preterm neonates, spastic diplegic CP is the most common subtype representing about three-fourths of those affected with CP. They typically have spasticity mainly in the lower limbs

and less evident in the upper limbs. This form is associated with injury to the internal capsules, which is primarily due to an ischemic injury that is associated with the radiological or pathological finding of periventricular leukomalacia ([PVL], i.e., the scarring of white matter around the cerebral ventricles, or secondary to severe intraventricular hemorrhage).[10,54,55] On the other hand, athetoid or dyskinetic CP is the second most common subtype associated with damage to the basal ganglia. However, damage to the cerebellum is associated with the ataxic CP subtype, the least common type. These subtypes occur in 12-14% and 4-13% of patients with CP, respectively. Both forms of CP can be associated with intellectual impairment, speech problems, and walking difficulties.[55] Also, CP can exist with other patterns of neurodevelopmental impairments as the presence of PVL can predict it.[56]

There is a higher risk of occurrence of CP in preterm infants than in full-term infants. In France, a cohort study reported that at the age of two years, infants born at 24 to 26 weeks and 27 to 31 weeks showed signs of motor impairment (17% and 10%, respectively). They also reported that the risk of CP was about 7% and 4%, respectively.[16] Another prospective cohort study assessing the prevalence of CP reported a 7% incidence in those born at <28 weeks compared to 0.1% in those born full-term.[17] In the Extremely Low Gestational Age Newborns (ELGAN) study, about 11% of the preterm infants born at <28 weeks' gestation met the criteria for CP.[57]

Preterm infants have more long-term serious outcomes than infants born full-term.[12] Indeed, it is reported that 25% of preterm infants have some significant neurodevelopmental impairments, identified at 18 to 24 months corrected age, including CP, sensory impairments such as hearing, and vision loss.[15,46,58,59] Brain maturation and cortical synapse formation show rapid growth during the final few weeks of pregnancy.[50] Therefore, being born prematurely alters brain maturation and development. Although the brain maturation of premature neonates continues after

birth, the circumstances in utero are tremendously different from the external adverse environmental conditions.[50,60] Significant neurodevelopmental impairment can be detected at 18-24 months in such at-risk infants. This period of development is one of the most common timepoint to classify the existence of moderate or significant neurodevelopmental impairment.[61,62]

8.1.5.3. *Hearing and vision impairments:*

Hearing and visual disabilities are common impairments associated with preterm birth. ROP is an abnormal vascularization of the developing retina of premature infants.[50] ROP is a multifactorial disease. Indeed, exposure to prolonged oxygen therapy, prematurity, abnormal growth, nutrition, and low birth weight are the main risk factors for this entity.[50,63] In ROP, an abnormal vascular response is described in 5 stages; total retinal detachment represents stage 5.[64] The untreated severe form of ROP, retinal detachment, leads to blindness, remaining a leading cause of total or near-total vision loss in childhood.[63,65] Among preterm infants, the incidence of bilateral blindness ranges from 0.6% to 1.6%.[49,66,67] Serenius *et al.* and Hintz *et al.* reported that the risk of blindness in preterm infants is higher compared with term infants, reaching 2.2% in neonates born at <25 weeks of gestation.[17,50,68] A meta-analysis including 21 studies assessing 190,946 preterm infants concluded that prematurity is associated with higher odds of ROP.[63] Some studies have described an association between exposure to maternal hypertension and an increased risk for severe ROP (OR: 2.0; 95%CI: 1.1–3.0).[69-71]

Hearing loss is attributable to several causes, including sensorineural and conductive anomalies, as well as auditory neuropathy.[72,73] The level of hearing loss is classified by measuring the ability to hear different sound frequencies and intensities. For instance, severe hearing loss can be defined as when the child cannot hear sounds below 71 dB.[72] Although auditory impairment may require hearing aids or cochlear implants; these devices may fail in children with profound

hearing loss (>90 dB).[42,74] Exposure to ototoxic medications such as aminoglycosides and furosemide may contribute to hearing disability.[69] The risk of hearing impairment in preterm infants is tenfold higher than in others.[75] Hintz *et al.* stated that the risk of deafness was 1.4% in infants born at 24–26 weeks.[68] In an Australian cohort study, the risk of deafness in preterm infants born at <25 weeks of gestation was 2.5%.[75] Therefore, preterm infants are more susceptible to hearing and vision impairment.[50] The evidence of hearing loss results has not yet been considered a potential complication from maternal hypertension.[76] A recent retrospective study concluded that this hearing defect was statistically significant, but it is a temporary effect related to prematurity.[77] Despite this, we can say maternal hypertension, particularly preeclampsia, can lead to hearing impairment by increasing the risk of premature birth.[76,77]

8.1.5.4. *Independent factors and neurodevelopmental outcomes:*

Many antenatal, perinatal, and postnatal factors can modulate the risk of NDI among term and preterm infants.[78,79] Notably, antenatal corticosteroids reduce the risk of CP and cognitive delay at two years of age.[78,80] As such, even a single course of antenatal corticosteroids seems to improve most neurodevelopmental outcomes in infants born before 34 weeks of gestation.[78,80] Sotiriadis *et al.* have reported that preterm neonates exposed to antenatal administration of corticosteroids for preterm labour experienced a lower incidence of cognitive delay.[80] On the contrary, postnatal exposure to corticosteroids has been associated with an increased risk of CP when administered in the first week of life and at a high dose.[81,82] Doyle *et al.* observed that although premature infants have an increased risk of BPD, they had increased survival rates free of CP after postnatal corticosteroid administration in those at higher risk for BPD.[13] In addition, a sick preterm infant with prolonged admission to neonatal intensive care is at a higher risk of developing neurodevelopmental impairments.[50]

8.2. Hypertensive disorders of pregnancy:

8.2.1. Definition and epidemiology:

Maternal hypertension is defined as at least two or more systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, at least 15 minutes apart, in a previously normotensive person.[83] The Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists have classified hypertensive disorders of pregnancy (HDP) as pre-existing (chronic) hypertension (hypertension before 20 weeks of gestation), gestational hypertension (hypertension that develops after 20 weeks of gestation), preeclampsia (gestational hypertension with proteinuria and/or other target organ involvement) and chronic hypertension complicated with preeclampsia.[83-85]

HDP occur in up to 10% of pregnancies and remain one of the leading global causes of maternal and neonatal morbidities and mortality.[9,86-88] It is estimated that 10 to 15% of approximately 500,000 women die of pregnancy-related deaths every year due to HDP.[89,90] Moreover, about half a million newborns die annually due to the complications of preeclampsia.[12] Due to socioeconomic, educational, and environmental difficulties in developing countries, women in these countries are at a greater risk of developing HDP than those in high-income developed countries, thus raising the maternal and fetal complications rates.[90] In developing countries, the World Health Organization estimates the incidence of preeclampsia to be seven times greater than in developed countries, 2.8% of live births and 0.4% respectively.[15,91] However, the incidence of eclampsia is the same and equals 5–7 cases per 10,000 deliveries in North America and Europe, while in developing countries, it ranges from 1 case per 100 to 1 case per 1700 pregnancies.[92,93] In the United States, in 2012, an epidemiological study reported that the expense of preeclampsia within the first year of delivery was $2.18 billion, almost divided equally between

mothers and infants.[94] Also, a 2016 study in the United States found that hypertension was the second most common complication that led to a postpartum hospital readmission.[95]

In utero exposure to a maternal hypertensive environment has been speculated to impact infant growth and brain development.[8-10] In Canada, HDP occur in about 7% of pregnancies and is responsible for a large portion of preterm births.[86] The early-onset type of maternal hypertension during pregnancy (that occurs after 20 weeks of pregnancy and <28 gestational weeks) is associated with a higher incidence of fetal growth restriction and NDI compared to late-onset hypertension in pregnancy.[96,97]

8.2.2. Pathophysiology of HDP:

HDP are multi-organ and multifactorial diseases causing endothelial cell dysfunction, inadequate and defective placentation, platelet and thrombin activation, autoimmunity, and inflammation.[98] The pathogenesis of hypertension in pregnancy, particularly preeclampsia, involves a combination of different genetic, structural, angiogenic, and metabolic pathways, including placental oxygenation, spiral artery remodelling, immune tolerance, and the equilibrium between angiogenic and antiangiogenic factors.[93] The increased incidence of neonatal morbidities and mortality is attributable to premature delivery and uteroplacental insufficiency, which causes diminished fetal blood flow, oxidative stress and prostacyclin and nitric oxide deficiency. These changes raise the endothelial sensitivity to vasopressor substances, platelet activity, and thrombogenesis, resulting in vascular endothelial dysfunction and functional impairment of other organs such as the placenta, the hematopoietic system, the brain, the kidneys, the liver, and the pancreas.[93] Hence, the pathophysiological characteristics of HDP in the mother and the fetus are demonstrated at two levels. First, at the local level, there is defective placentation and decreased placental perfusion.[93,98] Second, at the systemic level, there is vascular endothelial dysfunction and

imbalances in angiogenesis.[93] Therefore, the various clinical manifestations of HDP arise from the dysfunction of the placenta and the other body organs.

8.2.3. The impact of maternal hypertension on infant outcomes:

HDP are one of the most common disorders complicating pregnancy and leading to increased neonatal mortality and morbidities, including growth restriction, BPD, NEC, ROP, respiratory distress syndrome and hematological changes.[99] A prospective study on extremely premature infants showed that exposure to preeclampsia is independently associated with an increased risk for severe respiratory distress syndrome (aOR: 2.40; 95%CI= 1.76–3.29) and BPD (aOR:1.64; 95%CI=1.12–2.40) compared to non-exposed infants, as well as a higher risk of NEC (OR: 2.0; 95% CI=1.1–3.7).[99] Many researchers have evaluated maternal hypertension's impact on newborns' hematological profiles. A case-control study showed higher frequencies of polycythemia, neutropenia, and thrombocytopenia among neonates of hypertensive mothers compared with neonates of normotensive mothers (8%, 15%, and 38% vs. 0%, 2%, and 8%, respectively).[100]

Several epidemiologic findings indicated that HDP would contribute to a higher incidence of SGA (OR: 2.02; 95%CI: 1.84-2.22).[96,101]The SCOPE study, a prospective multicentre cohort study on 3513 nulliparous women, reported that almost 11% of SGA occurred in the presence of maternal hypertension.[102] However, Other studies have shown the correlation between HDP and SGA in infants <32 weeks, ranging from 11% up to 75%.[103,104] Also, SGA and prematurity are associated with an increased risk of neurodevelopmental disorders, with several impacts on language, cognitive, and motor abilities. [105,106]

Brain development in infants is a dynamic process, relying on maternal, placental and neonatal factors.[107] The literature shows a contradiction regarding whether and to what extent

infants' exposure to HDP is associated with early neurodevelopmental outcomes. Increasing evidence indicates that intrauterine exposure to HDP negatively impacts preterm infants' neurological outcomes, with an increased risk for CP, cognitive dysfunction, and low developmental quotient.[11,108,109] The odds of CP in infants of preeclamptic women is almost doubled (OR: 1.94; 95%C=1.25, 2.97).[110] Moreover, two meta-analyses described an increased risk for autism spectrum disorders or attention deficit or hyperactivity disorder in infants exposed to maternal hypertension.[111,112] HDP, particularly preeclampsia, is associated with an increased risk of language development impairment and lower neurocognitive functions.[113-116] In contrast, other studies report lower mortality rates and a lower incidence of brain complications in those exposed to maternal hypertension.[11,117,118] This discrepancy is more likely attributed to missing of maternal and neonatal characteristics such as type and severity of HDP, administration of magnesium sulfate and the causes of prematurity which can alter the study results. Also, two of these studies have used unstandardized and outdated definition of the exposure of interest (HDP), which may cause information bias.[117,118] Moreover, Gemmel *et al.* included databases from two different countries with different ethnicity, which contributed to variability in population characteristics impacting the study outcomes.[117] These studies may attribute the neuroprotective effect of HDP to increased glucocorticoid endogenous production in the HDP group due to intrauterine stress environment, magnesium sulfate therapy before delivery, and anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 may inhibit vascular endothelial growth factor protecting from IVH.[11] However, the overall neurological outcome of infants born to mothers with HDP is still not well established and might be impacted by other factors such as preterm delivery, BPD, IVH and PVL.[11,98] Early detection, prevention, and proper management of maternal hypertension may reduce hypertension's burden on women and offspring.

8.3. The Bayley Scales of Infant and Toddler Development, Third Edition:

Bayley-III is the most widely used standardized developmental assessment tool worldwide for children.[106,119] This screening instrument is widely used for assessing developmental functioning. It measures children's neurodevelopment from 1 month (16 days) to 42 months of age.[120] Therefore, Bayley-III is an end-point assessment measuring the risk of child developmental delay, which affects almost 15% of children worldwide.[121]

Bayley-III applies a sequence of play tasks and caregiver report questionnaires. This approach assesses the child's functional level throughout the different developmental domains. These domains include cognitive, language, and motor domains, which collect and conduct information through behavioural assessment and interaction of the child, and the last two scales are divided into more subsets. The language scale involves receptive and expressive language abilities, while the motor scale comprises fine and gross motor skills. In comparison, the remaining two domains are social-emotional and adaptive behaviour, assessed through parent's report.[106,119,122]

8.3.1. Bayley-III domains:

1- *Cognitive scale*: It is a 91-items evaluation that assesses play skills, information processing, processing speed, sensorimotor development, exploration of objects, object relations, concept formation, memory and problem-solving, such as placing blocks forming shapes, colour matching, and counting, solving complex patterns and pretense play.[119,122-126]

2- *Language scale*: includes the receptive and expressive communication subsets.

   a- Receptive subset: It is composed of 49-items assessing preverbal behaviour, including the capability to identify sounds and objects, morphological markers, vocabulary

development and measure children's social referencing, such as asking the child to identify objects from some pictures.[119,122-126]

b- Expressive subset: It is composed of 48-items assessing preverbal communication, including observing babbling, gesturing, and vocabulary use such as naming objects and sentence formation. Both subtests involve items assessing social abilities.[119,122-126]

3- *Motor scale:* includes the fine motor and the gross motor subsets.

a- Fine motor subset: It is a 66-items evaluation assessing skill related to visual tracking, object manipulation, functional hand skills, reaching and grasping, such as putting coins into a savings box, using scissors, and stacking blocks.[119,122-126]

b- Gross motor subset: It is 72-items evaluation assessing body control and movement, including head control, sitting, walking, static positioning, dynamic movement, and balance.[119,122-126]

4- *Social-Emotional Scale***:** Obtained from the Greenspan Social-Emotional Growth Chart,[127] consists of 35 items measuring emotional development and behaviour, such as using emotional signals purposefully to solve problems. The information is derived from the infant's caregiver.[119,124,126]

5- *Adaptive Behavior Scale:* consists of 241 items answered by the child's caregiver. These items are based on skill areas of communication such as speech and language, community use, health and safety, for instance, the ability to avoid danger, leisure, e.g. follow the rules, self-care and self-direction, letters identification, counting, and drawing.[119,124,126]

8.3.2. The Bayley-III scores interpretation:

Each test item has a scale score that determines infant performance. The composite score of Bayley-III is computed according to a comparison between the child and a normative sample matched with age. The language and motor composite scores result from sums of the subtest scale scores. However, the cognitive composite score is calculated from a single scale score. Composite scores vary from 40 to 160, with a score of 100 being the 50th percentile (score standard deviation is 15). The mean score indicates the child's mid-average functioning. The Bayley-III cognitive, language and motor scales' composite scores of 2 standard deviations below the mean, which corresponds to scores of less than 70, are commonly used as an indicator for significant (severe) developmental delay [125]. While the composite score of 1 standard deviation below the mean (less than 85, 16th percentile) indicates the presence of "any" neurodevelopmental impairment.[123] Eventually, the sum of scores of the domains classifies the performance into one of four categories of development: 1- accelerated development 2- within normal limits 3- at risk, and 4-delayed.[106,128]

8.3.3. Limitations of Bayley-III scales:

The Bayley-III is frequently criticized for its lengthy application time.[123] However, its architecture offers a flexible administration that meets a wide range of implementations. It may not be suitable for every application. Also, the norm sample did not include all special needs cases.[123,124] Furthermore, children with significant sensory impairments such as blindness and deafness, severe spinal cord injuries, and severe physical conditions may be prohibited because their illness may interfere with the appropriate administration.[123,124] The examiner should carefully choose the language of instructions and also be aware of body language.[123]

8.4. Summary and rationale:

Preterm birth is rising worldwide and is associated with poor neurodevelopmental outcomes. Maternal hypertension is a risk factor for preterm delivery and SGA, impacting infant neurodevelopment. Whether maternal hypertension itself contributes to NDI after accounting for prematurity and SGA is not well understood. Optimal management of maternal hypertension for child neurodevelopment as a potential strategy is similarly unknown. Therefore, in this thesis, we performed a study aiming to assess the association between exposure to maternal hypertension with/without SGA and the risk of NDI at 24 months of age among extremely preterm infants. We hypothesized that maternal hypertension is associated with poorer neurodevelopmental outcomes in these children after accounting for gestational age at birth and other factors.

9. OBJECTIVES AND HYPOTHESIS:

9.1. Primary objective:

Among a cohort of children born extremely preterm (<29 weeks of estimated gestational age at birth) who survived until their neonatal developmental follow-up appointment at 18 to 24 months corrected age, we aimed to assess the association between in utero exposure to maternal hypertension, compared with no such exposure, and the occurrence of *any NDI*.

Hypothesis: We hypothesized that maternal hypertension exposure was associated with a higher frequency of *any NDI* compared to those not exposed to maternal hypertension.

9.2. Secondary objectives:

a. To assess the association between exposure to maternal hypertension and the composite outcome of *significant NDI* at 18-24 months in the same cohort of extremely preterm infants.

   Hypothesis: We hypothesized that exposure to maternal hypertension was associated with a higher frequency of *significant NDI*.

b. To assess the association between exposure to maternal hypertension with/without SGA and the composite outcome of *any NDI* at 18-24 months in the same cohort.

   Hypothesis: We hypothesized that exposure to maternal hypertension with SGA was associated with a higher frequency of *any NDI*.

c. To assess the association between exposure to maternal hypertension with/without SGA and the composite outcome of *significant NDI* at 18-24 months in the same cohort.

   Hypothesis: We hypothesized that exposure to maternal hypertension with SGA was associated with a higher frequency of *significant NDI*.

10. PREFACE TO MANUSCRIPT:

Preterm birth accounts for up to 75% of neonatal mortality and 50% of morbidities such as NDI,[6] especially CP.[4] Infants born <29 weeks' gestation are at significant risk of CP, other NDI and behavioural disabilities.[5] Preterm newborns with concomitant SGA are at even higher risk of neonatal mortality and morbidities.[26]

Globally, up to a fifth of preterm births are due to hypertensive disorders of pregnancy (HDP).[7] HDP occur in up to 10% of pregnancies worldwide and is a risk factor for prematurity, IUGR, and being born small for gestational age (SGA).[129-131] In-utero exposure to an HDP environment has been associated with altered infant growth and brain development.[8-10] However, less is known about how maternal hypertension impacts childhood neurodevelopment after preterm birth.[11] Moreover, whether milder forms of maternal hypertension contribute to these adverse outcomes is not well described. We, therefore, performed a retrospective observational cohort study of extremely preterm infants. We sought to evaluate the association between exposure to maternal hypertension and the risk of any or significant NDI at 18-24 months corrected age in extremely preterm infants surviving until their follow-up evaluation.

This manuscript will be submitted to the American Academy of Pediatrics Journal (*Pediatrics)* and has been drafted following its guidelines. To our knowledge, this is the first study conducted using the MUHC and CHU-SJ's local databases to study the association between exposure to HDP and the risk of NDI in extremely preterm infants.

11. MANUSCRIPT:

Association Between Maternal Hypertension and Infant Neurodevelopment in Extremely Preterm Infants

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Abbreviations:
Adjusted odds ratio (aOR)
Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)
Cerebral palsy (CP)
Confidence interval (CI)
Gross Motor Function Classification System (GMFCS)
Neurodevelopmental impairment (NDI)

Premature rupture of membranes (PROM)
Small for gestational age (SGA)
The score for Neonatal Acute Physiology-II (SNAP-II)

Article Summary:
Maternal hypertension is a key factor that impacts the neurodevelopmental outcomes of extremely premature infants (<29 weeks), specifically if coincident with small for gestational age (SGA).

What's Known About This Subject:
Extremely preterm infants (<29 weeks) are at significant risk of neurodevelopmental impairment (NDI). Maternal hypertension is associated with preterm delivery and its sequelae, including NDI. Maternal hypertension's direct impact on NDI independent of prematurity is not well known.

What This Study Adds:
Extremely preterm infants exposed to maternal hypertension were more likely to have any NDI or cerebral palsy compared to similar gestational age infants exposed to a normotensive environment.

Contributors' Statement Page
Dr. Natalie Dayan conceptualized and designed the study, interpreted the results, and reviewed and revised all manuscript drafts for important intellectual content.
Dr. Gabriel Altit conceptualized and designed the study, designed the data collection instruments, interpreted results, and critically reviewed the manuscript for important intellectual content.
Drs. Richard Brown, Marc Beltempo and Anie Lapointe interpreted the results and critically reviewed the manuscript for important intellectual content.
Dr. Wael Abdelmageed conceptualized and designed the study, conducted the analyses, drafted the initial manuscript, revised the manuscript, and produced the final version.
All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Abstract:

Objectives: To assess the association between exposure to maternal hypertension and the presence/degree of NDI at 24 months in extremely preterm infants (born at <29 weeks of gestational age).

Patients and Methods:
This retrospective study used data from two neonatal units, and included infants born between 23^{+0} and 28^{+6} weeks from 2011 to 2017. Exposure was the presence of maternal hypertension with/without being born SGA. Outcomes were the presence of any or significant NDI; each was a composite, including elements derived from Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Logistic regression models assessed associations between maternal hypertension with/without SGA and NDI, adjusted for diabetes, gestational age, cesarean delivery or premature rupture of membranes.

Results:
Of 1019 preterm infants, we included 647 infants (median gestational age 26 weeks, interquartile range (IQR): 25-28), of which 96 (15%) were exposed to maternal hypertension and 71 (11%) exposed to hypertension and SGA. Infants exposed to maternal hypertension had higher rates of any NDI (n=55/96 [57%] vs. n=248/551 [45%]; adjusted odds ratio (aOR): 2.26; 95% confidence interval (CI)=1.39-3.72) and significant NDI (n=21/96 [22%] vs n=86/551 [16%]; aOR: 1.89; 95%CI=1.02-3.41). Maternal hypertension with SGA was more strongly associated with any NDI (aOR: 4.49; 95%CI=1.77-12.96) and significant NDI (aOR: 4.77; 95%CI=1.76-12.33).

Conclusion:
Maternal hypertension was associated with a higher risk of NDI in extremely preterm infants, particularly with SGA.

Introduction:

Beyond the neonatal period, up to 45% of children born preterm are subsequently diagnosed with cerebral palsy (CP), while up to 35% have visual impairment, and 25% have cognitive or hearing impairment.[18,24,25] As a result of these long-term consequences, prematurity is directly or indirectly associated with considerably high health care expenditures, reaching up to $25.2 billion in the USA in 2016.[23,41,132,133]

Extremely preterm infants (i.e., birth before 29 weeks of gestational age) are at particularly high risk of downstream cognitive and behavioral deficits and learning or motor disabilities. For example, the incidence of CP among children born <29 weeks is 4%, while it is 1% in infants born 32-34 weeks and 0.1% in children born at term.[5,16,17] Moreover, gestational age at birth is inversely related to the severity of NDI in childhood, with nearly 25-30% of extremely preterm infants being diagnosed with significant NDI (Bayley-III score <70, CP, blindness, or deafness requiring amplification) at 18 to 24 months. [17,42,59,134] Preterm infants who are also born SGA experience not only a higher risk of mortality but also an increased risk for behavioral disorders, cognitive delays and CP.[26,135-138]

Globally, up to a fifth of preterm births are attributable to hypertensive disorders of pregnancy due to both uteroplacental insufficiency and iatrogenic premature delivery.[7,9,86,87,93] Although infants born to hypertensive mothers have been noted to have abnormal neurological development,[8-10] the degree to which this is mediated by preterm birth versus other factors is not well understood. Exposure to a hypertensive environment in utero may directly impact an infant's neurodevelopment by altering placental blood flow, oxygenation, nutrition, and exposure of the infants to inflammatory agents, causing neuronal connectivity and myelination deficits exacerbated by hypoxia.[128,139-142]

We sought to assess the association between exposure to maternal hypertension and the risk of NDI at 24 months of age among extremely preterm infants. We hypothesized that maternal hypertension is associated with poorer neurodevelopmental outcomes after accounting for gestational age at birth and other factors.

Methods:

Study Design:

We performed a retrospective observational cohort study using data from two tertiary neonatal intensive care units in Montreal, Canada. We followed the "strengthening of reporting for observational studies in epidemiology" guidelines.[143] Research ethics board approval was obtained at both institutions (*McGill University Health Center* [MUHC] and *Centre hospitalier universitaire Sainte-Justine* [CHU-SJ]).

Data source and patient population:

We conducted this study using the data collected from the local MUHC and CHU-SJ neonatal databases. Although data is transmitted to the Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network for national cooperation, each local institution acts as the primary custodian of the data.[67,144,145] Maternal and neonatal data were entered electronically by trained abstractors using a customized data entry program. The data collected has standardized definitions using operations manuals across centres.[146-148]

A follow-up visit occurs at both institutions between 18 to 24 months of corrected age in all infants born at <29 weeks. These visits occur in specialized developmental clinics during which there is an assessment by an interdisciplinary team (pediatrician, occupational therapist and

physical therapist). Bayley-III is administered in both follow-up clinics to assess the infant's development. Bayley-III is a widely used developmental assessment tool and comprises cognitive, language, and motor composite scores.[106,119] Data from the Bayley-III was collected, as well as available follow-up data regarding hearing/visual impairment(s) and a diagnosis of CP (**Supplementary Table 1**). When CP was diagnosed, the gross motor functional classification scale [GMFCS] assessment was collected.[149,150]

Inclusion and Exclusion criteria:

We included infants born at 23^{+0} to 28^{+6} weeks of estimated gestational age, from January 2011 to December 2017, who were admitted to these centres within the first 24 hours of life and who attended their 18- to 24-month corrected age follow-up appointment. We excluded infants without information on maternal hypertension status, those with significant congenital anomalies or a genetic syndrome (which strongly influences our outcome of interest), those without any follow-up data, and those with a mortality outcome before the follow-up visit.

Exposure:

The exposure of interest was the occurrence of maternal hypertension during pregnancy as documented by a physician in the maternal medical chart. Because hypertensive disorders of pregnancy subtypes (i.e., preeclampsia/eclampsia, gestational hypertension or chronic hypertension in pregnancy) were not available in our database, we secondarily examined exposure to maternal hypertension with the presence of an SGA neonate as a proxy for a more severe subtype of hypertension.[151] This subgroup of infants was compared with non-SGA infants exposed to normotensive mothers.

Outcomes:

The primary outcome was the presence of *any NDI*. Any NDI was defined as the presence of at least one among: CP with a GMFCS of any grade, one of the composite score of the Bayley-III of less than 85, a sensorineural or mixed hearing loss or the presence of unilateral visual impairment.[25,52,146,147] This definition has been reported in previous prematurity-related literature.[146,147,152] The secondary outcome was the presence of *significant NDI*, defined as the presence of at least one among: CP with a GMFCS ≥3,4 or 5, one of the Bayley-III composite scores <70, the need for a hearing aid or a cochlear implant, or the presence of bilateral visual impairment.[146,147]

Demographic and clinical datapoints

We extracted from the database information on maternal age, mode of delivery (cesarean or vaginal), prolonged premature rupture of membranes (PROM, define as a duration of more than 24 hours), whether the mother attended prenatal care, the presence of maternal diabetes of any type during pregnancy (as documented by the maternal medical team), use of antenatal antibiotics, and use of antenatal steroids for fetal lung maturation. We extracted data on gestational age at birth in weeks, birth weight, infant sex, singleton status, SGA status (defined as being born <10th percentile for the estimated gestational age based on Kramer curve),[153] Apgar score at 5 minutes of life, the Score for Neonatal Acute Physiology-II (SNAP-II), outborn status, duration of hospital stay (days), surfactant administration, postnatal steroid exposure for pulmonary management, early-onset sepsis (culture proven), nosocomial infection (isolation of bacterial, fungal or viral organism from blood or cerebrospinal fluid in a symptomatic infant after 2 days of age), necrotizing enterocolitis

(defined as stage 2 or more as per modified Bell's criteria),[154] retinopathy of prematurity, bronchopulmonary dysplasia (oxygen or respiratory support at 36 weeks corrected age), and presence of a severe neurosonographic anomaly (defined as intraventricular hemorrhage Grade ≥3 or periventricular leukomalacia).

Statistical Analysis:

We used descriptive statistics to characterize the study sample. Continuous data were tested for normality using a Shapiro-Wilk test,[109,155] and considered non-normal if $p<0.05$. Continuous and categorical variables are described as mean (SD, standard deviation) or median (IQR), respectively. The baseline characteristics were compared according to maternal hypertension status, as well as the subgroups with/without SGA. We compared the primary and secondary outcomes between the hypertensive and normotensive groups. We also compared those exposed to hypertension with SGA to those not exposed to hypertension and born without SGA. We calculated crude and adjusted odds ratios (ORs) and 95%CI using logistic regression to estimate the associations between maternal hypertension and maternal hypertension with SGA and the outcomes (any or significant NDI). Variables adjusted for in our models were selected *a priori* and included maternal diabetes, gestational age at birth <26 vs ≥26 weeks, as well as either exposure to cesarian delivery (model 1) or exposure to PROM (model 2). Based on the literature, we considered these covariates to have a potential confounding effect since they are associated with an increased risk of the occurrence of both the exposures and outcomes.[156-163] For infants who attended their follow-up visit and had partial Bayley-III assessment scores but no evidence of NDI, we considered them not to have the outcome. However, these infants were re-classified as having NDI in sensitivity analysis and re-ran our models. Analyses were conducted using R (version 4.1.1)

and R-studio (version 1.4.1717, international open-source collaboration).

Power calculation:

This study is a retrospective study with a predetermined sample size. Our study power calculation is based on two studies conducted in Canada as part of the Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network.[67,164] These studies have identified that 45% of infants born at <29 weeks have NDI. Chen *et al.* reported that maternal hypertension led to a 30% increase in the population with NDI (OR:1.29; 95%CI=1.21–1.38).[165] Therefore, we hypothesized that infants exposed to maternal hypertension might encounter an increased rate of NDI by 30%, with an anticipated incidence of ~60% in the exposed group. With a two-sided alpha of 0.05, a sample size of 647 and a ratio of 5 unexposed to 1 exposed (i.e., exposure rate of 20%), our study was considered powered at 75%. The power calculation was conducted using https://clincalc.com/.

Results:

Study flow:

Of 1019 infants identified within the hospitals' databases, 372 were excluded from our cohort for the following reasons: 3 with unknown maternal hypertension status; 198 who died before their follow-up visit (of which 35 [22%] were exposed to maternal hypertension); 21 who had a major congenital defect or anomaly; 150 who did not have any neurodevelopmental follow-up information (out of which 25 [16%] were exposed to maternal hypertension). We included 647 extremely preterm infants in our analysis (median gestational age 26 weeks, IQR: 25 - 28): 96 (15%) exposed to maternal hypertension, 71 (11%) exposed to hypertension and SGA, 551 (85%) unexposed to maternal hypertension, and 523 (81%) unexposed to either maternal hypertension or

SGA (**Figure 1**). The 96 infants exposed to maternal hypertension were first compared to the 551 unexposed. Following that, the 71 infants exposed to hypertension and born with SGA were compared to the 523 unexposed and without SGA at birth.

Baseline characteristics:

Maternal and neonatal characteristics of maternal hypertension exposure, as well as by presence or absence of SGA status, are shown in **Table 1**. Compared with infants of normotensive mothers, infants exposed to maternal hypertension were born to older mothers more frequently by cesarian delivery and were less likely to have PROM and maternal diabetes. Also, they were delivered at later gestational age, more often SGA and singleton. Although complications of prematurity were almost similar in both groups, infants of hypertensive mothers had higher rates of bronchopulmonary dysplasia and surfactant administration usage. Infants exposed to maternal hypertension that had concomitant SGA were more likely to be delivered by cesarean section with less incidence of maternal PROM and diabetes. Also, they showed a higher risk for neonatal complications except for early onset sepsis and necrotizing enterocolitis when compared to those exposed to normotensive mothers and born at an appropriate weight for gestational age.

Exposure to maternal hypertension and association with neurodevelopmental impairment:

Compared with infants of normotensive mothers, infants exposed to maternal hypertension had higher rates of any NDI (n=55/96 [57%] vs. n=252/551 [46%]) and significant NDI (n=21/96 [22%] vs n=86/551 [16%]) (**Table 2**). They also had higher rates of CP, gastrostomy at 24 months and Bayley-III motor, cognitive and language domains composite scores <70 and <85. Exposure to maternal hypertension was accordingly associated with an increase in the odds of any NDI

(crude OR: 1.64; 95% CI =1.06-2.55 and aOR: [model 1: aOR: 2.06; 95% CI=1.26-3.38; model 2: aOR: 2.26; 95% CI=1.39-3.72]). Maternal hypertension was also associated with an increase in the odds of significant NDI in model 2 (aOR: 1.89; 95% CI=1.02-3.41) but not in model 1 (aOR: 1.52; 95% CI=0.82 -2.73) (**Table 3)**.

Exposure to maternal hypertension with concomitant SGA and association with neurodevelopmental impairment:

Compared with infants of normotensive mothers born without SGA, infants exposed to maternal hypertension with SGA had a higher rate of any (n=18 [72%] vs n=232 [44%]) and significant NDI (n=10 [40%] vs n=78 [15%]) **(Table 2).** Moreover, SGA children exposed to maternal hypertension had significantly higher rates of Bayley-III motor, cognitive and language domains composite scores <70 and <85, gastrostomy at 24 months and need for walking aids compared to non-SGA infants exposed to normotensive mothers. Logistic regression models showed that exposure to maternal hypertension with SGA was also associated with an increase in the odds of both any NDI (crude OR: 3.23; 95% CI=1.38-8.42 and model 2 aOR: 4.49; 95% CI = 1.77-12.96) and significant NDI (crude OR: 3.80; 95% CI = 1.60-8.69 and model 2 aOR: 4.77; 95% CI = 1.76-12.33) **(Table 3).**

Sensitivity analysis:

Of 647 infants in our cohort who attended the 24-month neurodevelopmental visit, 73 had missing all data on neurodevelopmental assessment elements (e.g., 86 missing data on Bayley-III cognitive composite score, 90 missing data on Bayley-III motor composite score, 92 missing data on Bayley-III language composite score). In our primary analysis, incomplete assessments without evidence

of NDI were classified as "normal." We reclassified those with incomplete neurodevelopmental assessment in a sensitivity analysis as having either any NDI or significant NDI and re-ran our models. In a sensitivity analysis, we reclassified those with incomplete neurodevelopmental assessment as having either any NDI or significant NDI and re-ran our models. The association between hypertension and any NDI were attenuated after re-classification (OR: 1.31; 95% CI = [0.84-2.06]), as well as for significant NDI (OR: 1.16; 95% CI = [0.72 – 1.83]) (**Supplementary Table 2**).

Discussion:

Summary of findings:

In this cohort of extremely preterm infants, we found that maternal hypertension was associated with an increased risk of any or significant NDI at 24 months corrected age after accounting for maternal diabetes, gestational age at birth, and PROM as potential confounders. Exposure to maternal hypertension with occurrence of SGA was further associated with an increase in the risk of any and significant NDI. The risk of significant NDI due to maternal hypertension was slightly attenuated in the model adjusting for caesarean delivery and other factors, indicating its importance as a confounder. Also, we found that language development is the highly affected domain among infants exposed to maternal hypertension with/without SGA. The association between hypertension and any or significant NDI were attenuated after re-classification according to incomplete neurodevelopmental assessment data. Because maternal hypertension causes placental dysfunction and hypoxemia, it is plausible that hypertension during pregnancy could be a risk factor for NDI in infants.[93] Our study suggested that the neurodevelopmental outcomes for infants born to mothers with hypertension with/without SGA

were worse than those not exposed to maternal hypertension among extremely preterm infants. Finally, our findings agreed with our hypothesis.

Maternal hypertension impacts infant brain development:

Uteroplacental hypoxia resulting from abnormal spiral artery remodelling early in placentation, occurring frequently in the context of maternal hypertension, may impair infant brain development.[93,98] Indeed, uteroplacental insufficiency increases oxidative stress and the release of circulating vasodilator prostacyclin, as well as leads to nitric oxide endothelial production deficiency. These result in a decreased perfusion of various organs in the fetus, which impacts growth and organic function during a crucial time of embryogensis.[93,166] Although the fetus attempts to compensate ("head-sparing" growth restriction) by redistributing blood flow towards the brain and by increasing erythrocyte production for better oxygen carrying capacity, poor fetal oxygenation may specifically lead to an altered fetal cerebral growth. This may in turn jeopardize cerebral integrity and lead to later motor impairment (manifested clinically as a NDI).[93] Indeed, brain structural and vascular anatomic alterations of infants born to hypertensive mothers have been reported in both human and animal studies.[142,167] Elevated circulating plasma levels of pro-inflammatory cytokines, most notably interleukin 6, have been reported in hypertensive mothers with an offspring affected by autism spectrum disorder, suggesting an inflammation-related modulation of neuronal damage, a phenomenon also described in animal models.[115,168,169] Further, the brain of mouse models exposed to a hypertensive gestational environment had structural anatomical alterations, leading to functional impairments.[167,170] These pathophysiological mechanisms align with our results reporting a higher occurrence of any or significant NDI in children exposed to maternal hypertension who are also born SGA. In our study, the birthweight

of infants born to mothers with hypertension and without hypertension was lower, as opposed to the findings of other researchers reporting similar birthweight in infants born to mothers with hypertension.[106] This difference is possibly explained by our selection of the extreme premature population (compared to term infants), a group that is particularly at risk for long-term adverse outcomes.

The effect of growth restriction on neurodevelopment:

Maternal hypertension is strongly associated with the occurrence of a SGA status, and growth restriction has also been associated with an increased risk for NDI.[98,155,171,172] As such, using magnetic resonance brain imaging, premature neonates with growth restriction have been described to have a smaller brain volume and gray matter compared to those born with a weight that is appropriate for gestational age.[173] Our results suggest that the additive effect of SGA on exposure to maternal hypertension and extreme prematurity further increases the risk of NDI, a concern that may be nested in the embryological origins.

Maternal hypertension and infant neurodevelopmental outcome beyond prematurity:

A previous large retrospective Japanese study of 43,854 infants evaluated the impact of maternal hypertension exposure on the medical and the neurological examinations, as well as on a parent-reported developmental questionnaire at 3-years of age. They described a two-fold higher risk of NDI among the infants (n= 1120) exposed to maternal hypertension.[98] After adjustments for gestational age at birth, the authors described only an increase in the risk of mental developmental abnormalities (aOR 1.80, 95% confidence interval 1.21-2.69), and not in motor developmental abnormalities. As such, while they have not specifically reported the outcome at

the extreme of prematurity, the effect of maternal hypertension on NDI seems to be consequential in other gestational age groups at a populational level. Also, only 60 infants in their cohort were born at <28 weeks of gestation, challenging the ability for stratified analysis by gestational age status. Another recent prospective study evaluating 4031 mother-infant dyads with the Chinese version of the Gesell Developmental Schedules reported that maternal hypertension exposure was associated with a higher risk of NDI in infants at the age of six month, adding to the mounting literature of the adverse effect of maternal hypertension on all newborns at large.[165] Results from a South American prospective study of 149 term infants using the Bayley-III were in a similar direction.[106] Our study adds to this growing body of literature by indicating that these associations persist even among extremely preterm infants, suggesting that the effect of hypertension is not solely mediated by prematurity. This provides insight about risk stratification when planning the ongoing follow-up and the screening for NDI in infants born at the extreme of prematurity.

Controversy in the literature:

Other studies have not shown this effect of hypertension on neurodevelopment. Two large cohort studies were conducted in Australia, assessing the association between maternal hypertension and infant neurodevelopment and behavioral isssues.[174,175] The study by Matic *et al.* was a large retrospective analysis of 2549 mother-infant dyads born <29 weeks from 1998 until 2004 with follow-up until age two years.[174] While these authors found no effect of maternal hypertension on neurocognitive issues, there were important differences in our studies that require mention: their definition of maternal hypertension included mothers with an increase in blood pressure by 25 mmHg, which may have resulted in misclassification of normotensive mothers as hypertensive; they used older tools for assessment of development that lacked assessment of motor

function (while in our study, CP drove the association more than cognitive impairment); they adjusted for different factors, including surfactant use, which we do not believe meets criteria for a confounder.[176]

A prospective cohort study conducted in 1998 had two equal groups of 107 infants born <32 weeks of gestation and stratified by the exposure to maternal hypertension. [118] They assessed infants' neurodevelopment based on medical history and the Griffiths scale, which are less sensitive and specific than the Bayley-III. These authors also included infants born at a later gestational age (less susceptible to NDI), used an outdated definition of hypertension, and an unclear assessment of NDI and also had a relatively small sample size compared to our cohort. A recent retrospective study in the US reported an association between maternal hypertension and language delay at two years (aOR: 2.22; 95% CI= 1.44–3.42) but no other impairments.[116] This study used a population of mothers including only women with subclinical thyroid dysfunction – a strong factor for neurodevelopmental issues, which may have biased the results towards the null.[177] Finally an English study showed a nonsignificant trend towards an increased risk of CP (aOR: 1.26; 95% CI= 0.43,3.68)[178] though they included non-severe community diagnoses of NDI which may have diluted their findings.

Overall, while the literature is mixed with regards to this question, our study used a contemporary high-risk cohort from two academic referral centres with robust outcome assessments, and showed similar trends to previous literature especially with regards to CP.

Strengths and limitations:

Our study has several strengths, including using a large number of extremely preterm infants from two high-level tertiary neonatal centres, with rich clinical data and usage of standardized

definitions. Clinical outcomes were assessed based on validated neurodevelopment tools. We acknowledge that there are limitations owing to this study's retrospective and observational nature, such as the inability to determine causation, residual confounding, possible misclassification, and missing information. The database lacked data on socio-economical status, which might affect our results. Infants in families with low socioeconomic status or low education levels are more likely to have less access to care.[179] There is a theoretical possibility that infants lost to follow-up may have altered our findings as infants with more impairment are more likely to attend their follow-up appointments, which may overestimate the infants' numbers with NDI. In the pre-analytical stage, we had planned to adjust for exposure to prenatal care as a social determinant of health. However, most of the mothers in our cohort were exposed to prenatal care (>95%), indicating that this factor was not a discerning measure of socio-economical deprivation in our cohort. We compared the infants who were lost to follow-up or died before follow-up, according to the exposure or not to maternal hypertension. Of the 150 infants lost to follow-up and 198 who died before follow-up, 25 and 35 infants, respectively, were born to hypertensive mothers. Both, the lost to follow-up and the died before the follow-up showed equal contribution in the hypertension and no-hypertension groups supporting that by excluding them there is no selection bias in our study. Maternal hypertension status was based on diagnosis by the clinical team, and we lacked granular information about its subtypes. Hence, according to ACOG and ISSHP's definition of preeclampsia, we examined maternal hypertension with SGA as a proxy for the more severe hypertensive disorder of pregnancy, such as preeclampsia. [113,115,180,181] Furthermore, we did not have data on delayed cord clamping, antenatal magnesium sulfate administration or timing of antenatal steroid administration. A Canadian study showed that among infants born at <29 weeks, exposure to at least 2 of these evidence-based practices was associated with decreased odds of

mortality and severe neurological impairments (aOR: 0.61, 95% CI: 0.43–0.88).[182-185] Thus, future studies should be conducted to evaluate the impact of these factors on the link between maternal hypertension and neurologic development in preterm infants. Increasing literature is being published around the adverse Doppler ultrasound profile regarding signs of cerebral blood flow redistribution in pregnancy complicated with placental insufficiency and intra-uterine growth restriction (IUGR).[186,187] Although we used SGA as a proxy of uteroplacental insufficiency in our study, we did not have Doppler ultrasound data available for evaluation. Whether cerebral circulation redistribution is an indicator depicting the severity of IUGR or acts as an independent risk factor for adverse outcomes is still uncertain. Moreover, whether it is helpful for clinical management or not, more studies are required on the impact of placental insufficiency in the context of maternal hypertension and its effect on infant neurodevelopmental outcomes.

Conclusion:

In our cohort of extremely preterm infants, maternal hypertension was associated with a higher risk of adverse neurodevelopmental outcomes, particularly among infants born SGA. Our findings outline the need for future evaluations of the impact of better control of maternal hypertension on improving the developmental trajectory of their offspring, specifically when they deliver extremely preterm. In the meantime, these infants should be cautiously followed and offered early intervention to maximize their neurodevelopmental potential.

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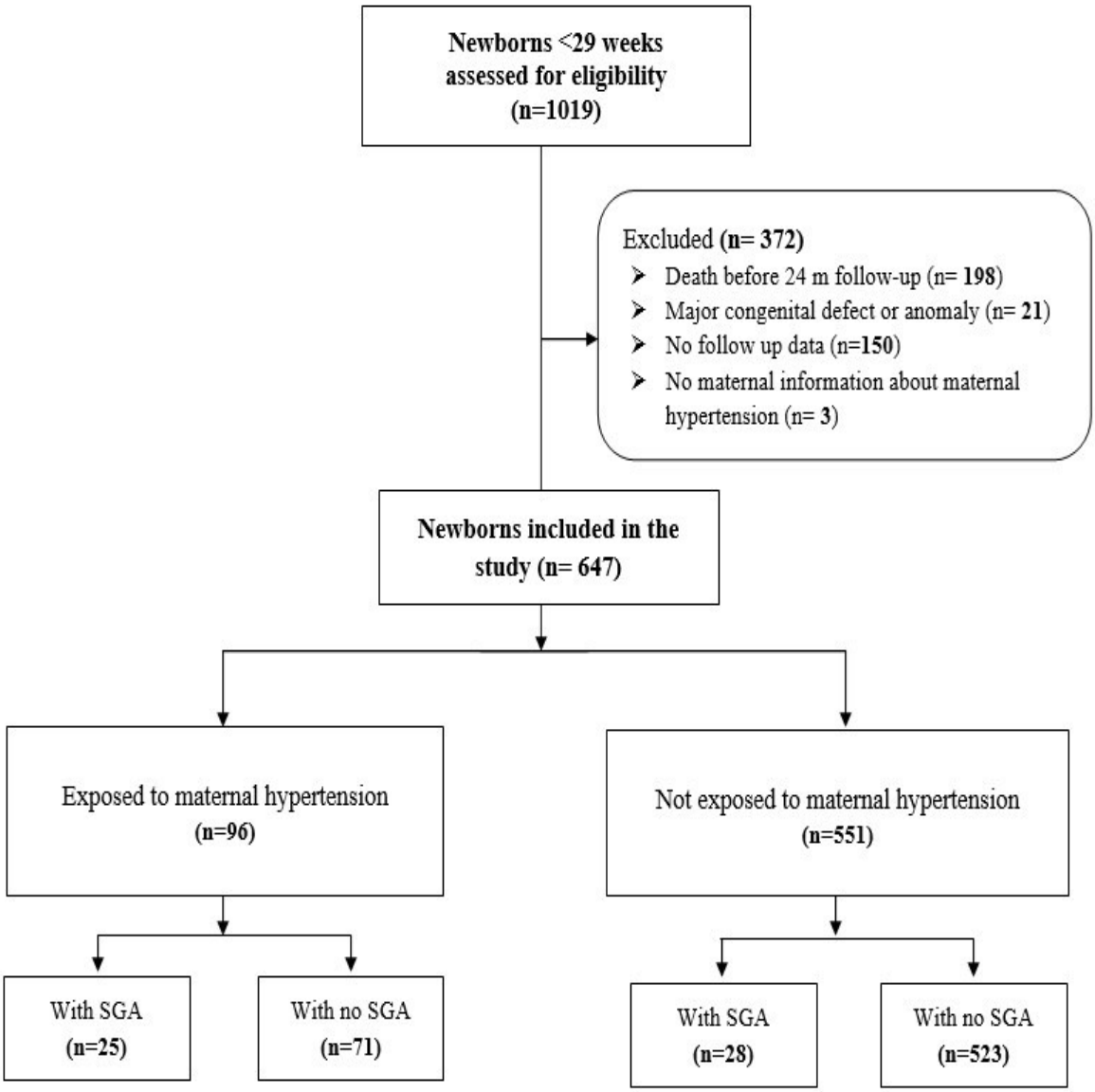
Fig. 1. Flow chart for participants' selection in this study.



Abbreviations: SGA: small for gestational age (defined as being born <10th percentile for gestational age based on Kramer curve[153]).

Table 1: Maternal and neonatal baseline characteristics of infants born < 29 weeks gestation, stratified according to the presence of maternal hypertension and SGA

Data expressed as n (%) unless otherwise indicated

	All Cohort n=647	Maternal Hypertension n = 96	No Maternal Hypertension n=551	Maternal Hypertension with SGA n= 25	No Maternal Hypertension and No SGA n= 523
Maternal characteristics:					
Age in years, mean (SD)	31.7 (6)	32.2 (6)	31.6 (5)	31.8 (6)	31.5 (5)
Cesarean section delivery	434(94)	90 (94)	344 (62)	25 (100)	319 (61)
Rupture of membranes>24 hours	204 (32)	7 (7)	197 (36)	0 (0)	187 (36)
Antenatal antibiotic use	453 (70)	33 (34)	420 (76)	6 (24)	405 (77)
Antenatal steroid use	604 (93)	94 (98)	510 (93)	24 (96)	482 (92)
Maternal diabetes	72 (11)	8 (8)	64 (12)	1 (4)	62 (12)
*Prenatal care**	630 (97)	94 (98)	536 (97)	23(92)	508 (97)
Neonatal characteristics:					
Gestational age at birth in weeks, median (IQR)	26 (25,28)	27 (26,28)	26 (25, 28)	27 (26,27)	26 (25,28)
≥23 to<26	194 (30)	12 (12.5)	182 (33)	2 (8)	174 (33.3)
≥26 to <29	453 (70)	84 (87.5)	369 (67)	23 (92)	349 (66.7)
≥23 to <24	15 (2)	0 (0)	15 (3)	0 (0)	15 (3)
≥24 to <25	84 (13)	5 (5)	79 (14)	1 (4%)	74 (14)
≥25 to <26	95 (15)	7 (7)	88 (16)	1 (4%)	85 (16)
≥26 to <27	130 (20)	21 (22)	109 (20)	7 (28%)	103 (20)
≥27 to <28	149 (23)	31 (32)	118 (21)	11(44%)	110 (21)
≥28 to <29	174 (27)	32 (33)	142 (26)	5 (20%)	136 (26)
Birth weight in grams	928 (230)	807 (199)	949 (229)	600 (81)	966 (221)
Female	307 (47)	46 (48)	261 (47)	14 (56)	247 (47)
Singleton	481 (74)	88 (92)	393 (71)	25 (100)	377 (72)
Apgar score at 5min<7	299 (46)	42 (44)	257 (47)	8 (32)	243 (46)
SNAPII score>20	168 (26)	20 (21)	148 (27)	5 (20)	137 (26)
Outborn	50 (8)	1 (1)	49 (9)	0 (0)	49 (9)
Duration of hospitalization, median (IQR)	100 (78,125)	102 (79,126)	100 (78,125)	123 (104,142)	98 (77,124)
Complications of prematurity:					
Surfactant exposre	422 (65)	78 (81)	344 (62)	19 (76)	322 (62)
Early-onset sepsis	16 (3)	0 (0)	16 (3)	0 (0)	15 (3)
Nosocomial infection	218 (34)	32 (33)	186 (34)	12 (48)	174 (33)
Necrotizing enterocolitis	55 (9)	7 (7)	48 (9)	0 (0)	45 (9)
Retinopathy of prematurity	82 (13)	11 (12)	71 (13)	5 (20)	64 (12)
Bronchopulmonary dysplasia	287 (44)	49 (51)	238 (43)	17 (68)	218 (42)
Intraventricular hemorrhage ≥Grade 3 or periventricular leukomalacia	73 (11)	9 (9)	64 (12)	4 (16)	63 (12)

Abbreviations: IQR: Interquartile range; SD: standard deviation; SGA: small for gestational age (defined as being born <10th percentile for gestational age based on Kramer curve);[153] SNAPII: the Score for Neonatal Acute Physiology-II.[144]

*prenatal care: defined as the mother had at least one prenatal care visit before delivery, or pregnancy is dated by ultrasound or if the mother had prenatal screens.[144]

Table 2: Frequency of any neurodevelopmental impairment, significant impairment, and their individual components among infants born <29 weeks gestation, stratified according to exposure to maternal hypertension and SGA.

Data expressed as n (%) or mean (SD) unless otherwise indicated

	All Cohort n=647	Maternal Hypertension n = 96	No Maternal Hypertension n=551	Maternal Hypertension with SGA n= 25	No Maternal Hypertension and No SGA n=523
Any NDI	303 (47)	55 (57)	248 (45)	18 (72)	232 (44)
Cerebral Palsy with GMFCS score of any grade (1 or higher)	39 (6)	11 (12)	28 (5)	2 (8)	28 (5)
Bayley-III Motor domain composite score < 85	146 (23)	31(32)	115 (21)	11 (44)	107 (20)
Bayley-III Cognitive domain composite score < 85	106 (16)	20 (21)	86 (16)	10 (40)	80 (15)
Bayley-III Language domain composite score < 85	208 (32)	40 (42)	168 (31)	16 (64)	154 (29)
Sensorineural/mixed hearing loss	56 (9)	3 (3)	53 (10)	0 (0)	50 (10)
Unilateral visual impairment	1 (0.2)	0 (0)	1 (0.2)	0 (0)	1 (0.2)
Significant NDI	107 (17)	21 (22)	86 (16)	10 (40)	78 (15)
Cerebral Palsy with GMFCS score of 3,4 or 5	14 (2)	1 (1)	13 (2)	0 (0)	13 (2%)
Bayley-III Motor domain composite score < 70	48 (7)	13 (14)	35 (6)	8 (32)	33 (6%)
Bayley-III Cognitive domain composite score < 70	20 (3)	7 (7)	13 (2)	5 (20)	12 (2%)
Bayley-III Language domain composite score < 70	67 (10)	13 (14)	54 (10)	6 (24)	49 (9%)
Hearing aid	6 (1)	0 (0)	6 (1)	0 (0)	5 (1%)
Bilateral visual impairment	7 (1)	0 (0)	7 (1)	0 (0)	6 (1%)
Tracheostomy at 18-24months	1 (0.2)	1 (1)	0 (0)	0 (0)	0 (0%)
Gastrostomy at 18-24 months	30 (5)	8 (8)	22 (4)	5 (20)	19 (4%)
Re-hospitalization	266 (41)	44 (46)	222 (40)	13 (52)	209 (40%)
Walking aids (stroller, walker or braces)	52 (8)	7 (7)	45 (8)	5 (20)	42 (8%)

Abbreviations: Bayley-III: The Bayley Scales of Infant and Toddler Development, Third Edition; GMFCS: gross motor functional classification scale; NDI: neurodevelopmental impairment.

Table 3: Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) from logistic regression models assessing the association between maternal hypertension and any or significant NDI.			
	Crude OR OR (95%CI)	**Model 1*** Adjusted OR (95%CI)	**Model 2*** Adjusted OR (95%CI)
Any NDI and hypertension	**1.64** **1.06-2.55**	**2.06** **(1.26-3.38)**	**2.26** **(1.39-3.72)**
Significant NDI and hypertension	1.51 0.87-2.55	1.52 (0.82 -2.73)	**1.89** **(1.02-3.41)**
Any NDI and hypertension with SGA	**3.23** **(1.38-8.42)**	**3.98** **(1.56-11.48)**	**4.49** **(1.77-12.96)**
Significant NDI and hypertension with SGA	**3.80** **(1.60-8.69)**	**3.58** **(1.33-9.15)**	**4.77** **(1.76-12.33)**

Abbreviations: CI: Confidence interval; NDI: neurodevelopmental impairment; OR: Odds ratio.
*Model 1: adjusted for Maternal diabetes, gestational age groups <26weeks and ≥26weeks, and Cesarean section.
*Model 2: adjusted for Maternal diabetes, gestational age groups <26weeks and ≥26weeks, and premature rupture of membranes >24 hours.

SUPPLEMENTARY TABLES:

Supplementary Table 1: Definitions of primary and secondary outcomes:

Domain	Primary outcome: Any neurodevelopmental impairment	Secondary outcome: Significant neurodevelopmental impairment
Motor	Cerebral palsy with GMFCS 1 or higher Bayley-III score <85	Cerebral palsy with GMFCS 3,4 or 5 Bayley-III score <70
Cognitive	Bayley-III score <85	Bayley-III score <70
Language	Bayley-III score <85	Bayley-III score <70
Hearing	Sensorineural or mixed hearing loss	Hearing aid or cochlear implant
Vision	Unilateral visual impairment	Bilateral Visual impairement

Abbreviations: Bayley-III: The Bayley Scales of Infant and Toddler Development, Third Edition; GMFCS: gross motor functional classification scale.

Supplementary Table 2*:* Univariate logistic regression analysis comparing missing data by considering as normal vs abnormal.						
Neurodevelopmental outcome	**Missing data is considered as "Normal"**			**Missing data is considered as abnormal "NDI"**		
	OR	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Any NDI	**1.64**	**1.06- 2.55**	**0.03**	1.31	0.84-2.06	0.24
Significant NDI	1.51	0.87-2.55	0.13	1.16	0.72- 1.83	0.54

Abbreviations: CI: Confidence interval; NDI: neurodevelopmental impairment; OR: Odds ratio.

12.DISCUSSION:

Summary:

In this thesis, we studied the association between exposure to maternal hypertension and the presence/degree of NDI at 18-24 months corrected age in extremely preterm infants. Our retrospective study used data collected from clinical databases of the local MUHC and CHU-SJ neonatal units, which are relatively large tertiary referral centres in Montreal. The Neonatal Intensive Care Unit (NICU) of the MUHC is a 52-bed referral center admitting 900 neonates per year. Similarly, the CHU-SJ's NICU is a 65-bed center which treats 1100 neonates annually. Together, we include 647 infants born between 23+0 and 28+6 weeks and admitted between 2011 and 2017 into our study. We found an increased rate of any and significant NDI, in particular (CP), in infants exposed to maternal hypertension. Further, the presence of SGA status at birth, a proxy for more significant maternal hypertension, also was associated with an even further risk for long-term NDI in this vulnerable population of infants.

In our manuscript (section 12 of the thesis), we explored how our results corresponded, as well as contrasted, with the current knowledge reported in the scientific literature. Further, we also discussed a few avenues explaining why maternal hypertension may significantly impact long-term outcomes in this population of infants. We believe that the increased prevalence of neonatal morbidities, particularly long-term NDI, is attributable to premature delivery and uteroplacental insufficiency. Placental dysfunction is at the cornerstone of the pathophysiology of maternal hypertension. Although many researchers have evaluated maternal hypertension's impact on an infant's neurodevelopmental outcomes, there is still a controversy surrounding the independent association between different types of maternal hypertension and the offspring's

neurodevelopment. We described here an association between the exposure to hypertension during pregnancy and the presence of NDI in a population of extremely premature infants. Many studies are in agreement with our findings[114,115] but had not previously described this effect in the extremely preterm infants. This finding was also replicated in the studies of Sala *et al.* and Chen *et al*[106,165]., but at the age of 6 months. Although all previous studies included infants of all ages, our results suggest that the adverse neurodevelopment of extremely premature infants may also be modulated by the exposure to maternal hypertension and the occurrence of concomitant SGA status. As such, this provides an opportunity for risk profiling in the premature infant at risk of developmental deficit, in order to detect NDI at earlier stages and provide optimal opportunities for rehabilitation and prevention.

Hypertensive disorders of pregnancy subtypes (i.e., preeclampsia and chronic hypertension in pregnancy) were unavailable in our database. According to the American College of Obstetricians and Gynecologists (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP), the presence of SGA is now one of the fundamental criteria of preeclampsia.[180,181] In a recent prospective study conducted in the UK following the ISSHP criteria considered a diagnosis of preeclampsia as hypertension with SGA fetus.[188] In 2022, a multinational study that obtained data from Denmark, Finland, and Sweden to examine the association between preeclampsia and risks of ischemic heart disease in infants, the study team considered preeclampsia with SGA birth as proxy marker of preeclampsia severity.[189] Other studies have described an association between preeclampsia and SGA, with up to a fourfold increased risk compared to normotensive mothers.[96,190,191] Therefore, we secondarily examined exposure to maternal hypertension with an SGA neonate as a proxy for a more severe hypertension subtype.

In our primary analysis, children who attended their follow-up visit and had incomplete neurodevelopmental assessments without evidence of NDI (i.e., did not meet the composite definition of NDI) were classified as "normal", i.e., free of NDI. Understanding that some of the missing information may have resulted in misclassifying some individuals as normal when they may have had NDI, we reclassified those children in sensitivity analyses as having either any NDI or significant NDI and re-ran our models. The association between hypertension and any NDI was attenuated after re-classification (OR: 1.31; 95% CI = [0.84-2.06]), as well as for significant NDI (OR: 1.16; 95% CI = [0.72 – 1.83]), Supplementary Table 2. We also performed a "complete case" analysis among the 554 infants with complete neurodevelopmental assessments and re-ran our primary models. The results showed that exposure to maternal hypertension was associated with a 2.2-fold increase in the risk of any NDI (aOR: 2.26; 95% CI=1.39-3.72]) and 1.9-fold risk of significant NDI (aOR: 1.89; 95% CI=1.02-3.41) (Table 3). Additionally, the missing data was mainly (90%) found in the non-hypertensive group. Based on our sensitivity analyses, we can assume that the true estimate is somewhere between 1.30 and 2.2 for any NDI and 1.1 and 1.9 for severe NDI.

Previous literature:

Some studies have described contradictory findings regarding whether or not infants' exposure to maternal hypertension is associated with their neurodevelopmental outcomes.[98,116] Noda *et al.* and Palatnik *et al.* reported an increased risk of mental developmental abnormalities (aOR: 1.80; 95%CI=1.21–2.69) and language delay (aOR: 2.22; 95% CI=1.44–3.42), respectively.[98,116] These studies included a high participation of full-term infants (who have a low baseline susceptibility for neurodevelopmental impairments) have not found an association

between maternal hypertension and offspring's neurodevelopment. Noda *et al.,* was also affected by a low rate of follow-up, as well as with a low inclusion of preterm infants, resulting possibly in selection bias. Our analyses were not affected by substantial missing data (<10%).[98] In our cohort, infants that were lost to follow-up or died prior to their follow-up evaluation were proportionally similar in terms of exposure to maternal hypertension to our analyzed cohort, indicating that there is unlikely a differential loss to follow-up.

Studies that showed no association between maternal hypertension and impaired infant neurodevelopment or reported an infant neuroprotective effect of maternal hypertension were small in sample size.[117,118] They defined NDI using less standardized tools and did not account for some confounders, such as gestational age. Our study used a sizeable database of extremely premature infants composed of two high-volume centres, with robust definitions and outcomes assessment by certified teams performing neurodevelopmental assessments. Consequently, our study is unlikely to have non-differential misclassification or selection biases.

Thesis limitations:

Our study was an observational retrospective study and, as such, has limitations that must be considered. A discussion of these biases follows below.

1. Misclassification bias:

As our exposure and outcomes were retrospectively assessed by different medical staff, as well as infants' neurodevelopment assessment may be affected by the individual judgment, and inter-rater variability is possible. Given that neurodevelopmental assessment was done by local,

highly qualified, trained experts (pediatricians, occupational therapists and physical therapists) using the Bayley-III, the most widely used standardized development assessment tool worldwide[106,119] this variability is expected to be minimal. We think any misclassification of the outcome is likely to be non-differential, as the assessment was done without consideration of the impact of maternal hypertension status.

2. Confounding bias

Observational studies are prone to bias due to residual confounding. Confounders might account for disturbed associations. However, we performed a DAG, and then we studied the relationship between exposure, outcome, and other covariates. We proposed the plausible potential confounders to adjust for them based on the literature.

3. Missing data:

Missing data can be problematic in observational studies, especially if data are missing not at random. Fortunately, our analyses as well as outcomes were not affected by substantial missing data, so this was unlikely a significant contributor to bias in our study. Also, we compared the infants lost to follow-up or died before follow-up according to their exposure to maternal hypertension. We found that those infants contribute the same portion for both hypertensive and no-hypertensive groups. Thus, we do not think critical missing bias has impacted our results.

CONCLUSION:

In our cohort of extremely preterm infants, maternal hypertension was associated with a higher risk of adverse neurodevelopmental outcomes, particularly among infants born with SGA. Our findings outline the need for future evaluations of the impact of better control of maternal hypertension on improving the developmental trajectory of their offspring, specifically when they deliver extremely preterm. In the meantime, these infants should be cautiously followed and offered early intervention to maximize their neurodevelopmental potential.

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14.APPENDIX:

Supplementary Table 1: Definitions of primary and secondary outcomes:		
Domain	Primary outcome: Any neurodevelopmental impairment	Secondary outcome: Significant neurodevelopmental impairment
Motor	Cerebral palsy with GMFCS 1 or higher Bayley-III score <85	Cerebral palsy with GMFCS 3,4 or 5 Bayley-III score <70
Cognitive	Bayley-III score <85	Bayley-III score <70
Language	Bayley-III score <85	Bayley-III score <70
Hearing	Sensorineural or mixed hearing loss	Hearing aid or cochlear implant
Vision	Unilateral visual impairment	Bilateral Visual impairement

Abbreviations: Bayley-III: The Bayley Scales of Infant and Toddler Development, Third Edition; GMFCS: gross motor functional classification scale.

Supplementary Table 2*:* Univariate logistic regression analysis comparing missing data by considering as normal vs abnormal.						
Neurodevelopmental outcome	**Missing data is considered as "Normal"**			**Missing data is considered as abnormal "NDI"**		
	OR	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Any NDI	**1.64**	**1.06- 2.55**	**0.03**	1.31	0.84-2.06	0.24
Significant NDI	1.51	0.87-2.55	0.13	1.16	0.72- 1.83	0.54

Abbreviations: CI: Confidence interval; NDI: neurodevelopmental impairment; OR: Odds ratio.