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Title: The causal effect of being born extremely preterm or extremely low birthweight on neurodevelopment and social-emotional development at 2 years

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Short title: Causal effect of extreme prematurity on neurodevelopment

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ABSTRACT

AIM

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To assess the causal effect of being born extremely preterm (EP; <28 weeks' gestation) or extremely low birthweight (ELBW; <1000 g) compared with being born at term on neurodevelopment and social-emotional development at 2 years' corrected age.

METHODS

Prospective geographical cohort study of children born EP/ELBW over 12 months in 2016 from Victoria, Australia, and term-born controls. Children were assessed at 2 years' corrected age with the Bayley Scales of Infant and Toddler Development-3rd edition and the Infant-Toddler Social and Emotional Assessment. Delay was defined as <-1 standard deviation relative to the mean of controls. The estimand of interest was the mean difference/odds ratio (OR) between the EP/ELBW and control groups estimated using linear/logistic regression, adjusted for multiple pregnancy and social risk.

RESULTS

205 EP/ELBW and 201 controls were assessed at 2 years. Delay/concerns were more common in the EP/ELBW group compared with controls, for cognitive (OR 3.7 [95% confidence interval 2.3, 6.0]), language (5.3 [3.1, 9.0]) and motor (3.9 [2.3, 6.3]) development, and social-emotional competence (4.1 [1.6, 10.2]).

CONCLUSION

Being born EP/ELBW has an adverse effect on cognitive, language and motor development, and social-emotional competence at 2 years' corrected age. Close developmental surveillance, including social-emotional development, is recommended.

KEYWORDS

Causal effect
Extremely preterm
Extremely low birthweight
Neurodevelopment
Social-emotional assessment

KEY NOTES

- We investigated the causal effect of being born extremely preterm/extremely low birthweight on cognitive, language, motor, and social-emotional development at 2 years' corrected age

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- Being born extremely preterm/extremely low birthweight has an adverse causal effect on neurodevelopment as well as social-emotional competence and behavioural regulation at 2 years' corrected age
- Further research on the causal effect of extremely preterm/extremely low birthweight birth on longer term outcomes is recommended
-

INTRODUCTION

As survival rates for children born extremely preterm (EP; <28 weeks' gestation)/extremely low birthweight (ELBW; <1000 g birthweight) have increased over time,[1, 2] it is important to understand the effects of being born EP/ELBW on children's neurodevelopment and social-emotional development, both for families and for services that provide care. Developmental follow-up for children born EP/ELBW should be an integral part of their clinical care. A detailed neurodevelopmental assessment gives families specific information for supporting their child's development through anticipatory guidance,[3] as well as a pathway to early intervention following identification of any delay or disability.[4] At a service level, understanding the effect of being born EP/ELBW on developmental outcomes is needed to evaluate and inform ongoing clinical practice and to counsel families.[4-6]

Follow-up of EP/ELBW children varies between centres, including the timing of assessments and developmental domains measured. Many services include assessment for cerebral palsy and general development up to 2 years of age, but it is less common for behavioural and social-emotional outcomes to be assessed, particularly in the first 2 years.[4] Given the increased rate of attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and childhood anxiety disorder in children born EP/ELBW[7] compared with term-born children, the assessment of behaviour and social-emotional development in early childhood in EP/ELBW children may increase understanding of, and help guide intervention for, these and related disorders.

Population-based cohort studies provide an opportunity to examine the development of EP/ELBW children compared with term-born controls.[8] Longitudinal studies have demonstrated that higher rates of cognitive difficulties,[9] motor impairment[10] and behavioural issues[11] in the EP/ELBW population are evident from childhood into adulthood, despite advances in clinical care.[1, 4, 9, 12] Lacking to date are population-based studies using a causal inference approach to adjust appropriately for confounding variables, such as multiple pregnancy and social risk factors, which may offer insight into the casual effect of being born EP/ELBW on key developmental outcomes.

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The aim of the current study was to assess the causal effect of being born EP/ELBW compared with being born at term on neurodevelopment and social-emotional development at 2 years' corrected age. We hypothesised that children born EP/ELBW would have higher rates of cognitive, motor and language developmental delay and disability, as well as poorer social-emotional and behavioural development, compared with term-born controls.

METHODS

Participants

Participants were recruited over a 12-month period as part of the Victorian Infant Collaborative Study (VICS) 2016-17 cohort which comprised all EP/ELBW infants who were born in the state of Victoria, Australia, between 1st April 2016 and 31st March 2017, and offered intensive care in one of the four neonatal intensive care units in the state. Contemporaneous healthy term-born controls (37-42 weeks' gestational age) with normal birthweight (>2499 g) were also recruited from the three perinatal centres in the state that were co-located with a tertiary neonatal intensive care unit.

Detailed perinatal data were collected, including gestational age, sex, birthweight z-score,[13] plurality, surgery, oxygen requirement at 36 weeks, and major brain injury including intraventricular haemorrhage (IVH) and cystic periventricular leukomalacia (cPVL). Social-demographic data were also collected, including language spoken at home (English only vs other) and non-private health insurance status as a proxy for social risk. The study was approved by the Human Research Ethics Committees at The Royal Children's Hospital, The Royal Women's Hospital, Monash Health and Mercy Health, and parents of all participants provided written informed consent.

Outcome assessment at 2 years' corrected age

At 2 years' corrected age, children attended a neurodevelopmental assessment at one of the participating tertiary centres. A paediatrician assessed children for neurosensory impairment including deafness (hearing loss requiring amplification or worse), blindness (vision <6/60 in the better eye) and cerebral palsy (abnormal tone or tendon reflexes, and loss of motor function).

Cognitive, language and motor development were assessed using the Bayley Scales of Infant and Toddler Development-3rd edition (Bayley-III)[14] by an accredited health professional unaware of the child's gestational age and perinatal history. The language scale was not administered to children who required an interpreter due to concerns about validity

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of English language assessment. As the Bayley-III has been shown to underestimate delay in the Australian population,[15] we used the term controls' mean score and standard deviation (SD) to calculate cognitive, motor and language delay defined as <-1 SD relative to the control group mean. Children who were unable to complete testing due to severe developmental delay were assigned a score of -4 SD, as per previous cohorts.[8] Rates of overall developmental delay, defined relative to the mean scores of the cognitive and language scales of controls, have been reported at 2 years' corrected age for children born EP only from the same cohort.[12]

Social-emotional and behavioural status was evaluated using the parent form of the Infant-Toddler Social and Emotional Assessment (ITSEA),[16] which assesses social-emotional behaviour and competence in children (age range 12 to 36 months). The ITSEA has 4 domains (externalising, internalising, dysregulation and competence) with raw scores converted to t-scores (mean 50, SD 10), and was scored according to the manual's published age and sex norms.[16] Parents completed the ITSEA online in English. T-scores at or above 65 on the externalising, internalising, and dysregulation domains, and at or below 35 on the competence domain are considered "of concern". The ITSEA has robust psychometrics[16] and has been used in studies of infants born preterm.

Statistical analysis

Data were analysed using Stata 16 (StataCorp, Texas, USA). A DAG-informed (directed acyclic graph) regression modelling approach was employed, which has been recommended as a causal inference tool. The DAG in Figure 1 outlines the causal assumptions made in the analysis. The estimands of interest were the mean differences and the odds ratios (OR) between the two birth groups for the continuous and binary outcomes, respectively, estimated via regression models fitted using generalised estimating equations to account for clustering of multiple births within the same family. Linear regression was used for Bayley-III continuous scores (composite and subscale scores) and the ITSEA t-scores (based on the published norms[16]). Logistic regression was used for any cognitive, language or motor delay (as well as delay on the receptive and expressive language and fine and gross motor subscales), and ITSEA "of concern" cut-off scores. Based on the assumed DAG, the models were adjusted for the confounding factors of social risk (private health insurance status, English only spoken at home) and multiple pregnancy. Results are presented with 95% confidence intervals (CI) and the corresponding p-values, with a focus on the overall strength of the evidence for differences between groups. As a sensitivity analysis, we conducted post-hoc analysis firstly excluding participants with neurosensory impairment (cerebral palsy, deafness or blindness) and then also excluding children with IVH or cPVL.

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RESULTS

Four hundred and sixty-five children were recruited into the VICS 2016-17 cohort, with 238 EP/ELBW children surviving at 2 years. Four hundred and twenty children were assessed at 2 years' corrected age, representing a 92% follow-up rate of recruited surviving EP/ELBW, and 90% of term controls (Figure 2). Two hundred and five children born EP/ELBW (EP n=165, ELBW not born EP n=40) and 201 term controls had social risk and 2-year assessment data and were included in this analysis (97% of those assessed). Participant characteristics for the 406 included children are summarised in Table 1. There was a higher proportion of multiple births in the EP/ELBW compared with the control group. A higher proportion of controls spoke only English at home, with similar rates of private health insurance in both groups. For the ITSEA, 21% of respondents spoke a language other than English at home, compared with 57% of non-respondents. The average age at follow-up assessment (corrected for prematurity) was similar between the EP/ELBW and control groups. Cerebral palsy was diagnosed in 13 (6.4%) of the children born EP/ELBW; of these children, one was also blind and deaf, and another was deaf. There was one child born EP/ELBW with isolated deafness. Of the two term controls with neurosensory deficits; one had cerebral palsy, and another was deaf.

For children born at term, mean scores for all Bayley-III scales were well above the normative means as expected, while children born EP/ELBW performed more poorly than term controls on all domains (Table 2). The causal relationship between birth group and outcome was strongest in the language domain with a mean difference exceeding 1 SD, with similar group differences for the receptive and expressive communication subscales. The ITSEA was completed for 61% of children born EP/ELBW and 82% of term-born controls. There was strong evidence of a causal relationship between being born EP/ELBW and poorer social-emotional competence and higher dysregulation, but little evidence for externalising or internalising problems (Table 2).

There was strong evidence of a causal relationship between being born EP/ELBW and higher odds of cognitive, language and motor delay compared with term-born controls, with close to 50% of EP/ELBW children delayed on most of the domains assessed (Table 3). The odds of poorer social competence were substantially higher in the EP/ELBW group compared with the term controls. Excluding 16 children with cerebral palsy, deafness or blindness, did not alter any conclusions. When a further six children who had major IVH or cPVL were excluded, the conclusions were similar except that the evidence for a relationship with dysregulation weakened (Supplementary Tables 1-4).

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DISCUSSION

Our findings suggest that being born EP/ELBW has a causal relationship with poorer cognitive, language and motor development, and behavioural regulation at 2 years' corrected age, with children born EP/ELBW having higher rates of delay or problems on these domains than term-born controls. Concerning neurodevelopment, one-half of the children born EP/ELBW had delayed cognitive development at 2 years' corrected age, which was four times the odds compared with controls. The causal relationship was also apparent in the continuous scores, in particular on the language and motor composite scores, and points to the adverse effect of being born EP/ELBW on all developmental domains assessed. The mean difference between groups was more than 1 SD on the language scale, with increased odds of receptive and expressive language delay in the EP/ELBW group compared with term controls.

Cognitive difficulties are common in children born EP/ELBW and our findings of high rates of cognitive delay are similar to other studies at 2 years' corrected age.[17, 18] Longitudinal studies of children born EP/ELBW have shown that cognitive difficulties, such as executive dysfunction, can persist into childhood and adolescence,[19] increasing risk for poor academic performance. Identification of children with cognitive delay at 2 years, can help with linking them in with intervention services prior to school entry, and ensure that children have appropriate support.

On language outcomes at 2 years, The Extremely Preterm Infants in Sweden Study (EXPRESS) had similar findings to our study, with the highest rates of delay on the language and fine motor subscales compared with term controls, and 14.9% and 14.5% with moderate-severe delay on the receptive and expressive communication scales, respectively.[18] In a study from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network in the USA,[20] 55% of ELBW children had receptive language delay and 26% had expressive language delays at 2.5 years. Children with language delay were more likely to also have feeding difficulties than those without a language delay. Language difficulties have been shown to persist into later childhood for many children born EP/ELBW. In a study of children born <26 weeks in the United Kingdom (EPICure study),[21] children had increased odds of language problems (OR 10, 95% CI 3, 32) and speech problems (OR 4.4, 95%, 3, 7) at 6 years compared with their term-born classmates. Studies of language trajectories of children born <30 weeks' gestation have demonstrated that generalised language difficulties persist from 2 to 13 years, with little evidence that children born preterm catch up with term-born controls.[22]

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The mean difference between EP/ELBW and term controls on the motor composite score in the current study was also marked, 0.8 of a SD, with almost 50% of the EP/ELBW group having a motor delay, and increased odds of fine and gross motor delay compared with term controls. There is evidence in longitudinal studies that even though rates of cerebral palsy have decreased over time for children born EP/ELBW, there has not been a corresponding decrease in the prevalence of motor impairment.[10, 23, 24] Motor impairment can affect a child's participation in daily activities, and has also been associated with social and behavioural difficulties in children born EP/ELBW,[24] underscoring the importance of early identification and intervention for not only cerebral palsy but also other motor impairment and delays.

In the current study, children born EP/ELBW had higher dysregulation and lower social-emotional competence than term controls, with the difference most marked in the competence domain of the ITSEA. The odds of delayed social-emotional competence was increased in children born EP/ELBW compared with controls, indicating the need for enhanced surveillance and intervention when indicated, in the EP/ELBW population. The competence domain includes subscales such as attention, imitation/play and prosocial peer relations. These skills underpin learning and social interaction, and difficulties in these areas may also indicate early signs of developmental disorders such as ADHD and ASD. Other studies of children born EP or ELBW have also found high rates of social-emotional competence difficulties. A study of children born EP at 18-22 months (n=2505) found that 26% had delayed social-emotional competence, and 35% had behavioural problems (a classification which includes internalising and externalising behaviours).[25] In another study of children born ELBW at 2-3 years (n=696),[26] 20% had delayed social-emotional competence, and over half had either behavioural or social-emotional competence problems. The EXPRESS study from Sweden also reported that children born <27 weeks' gestation had higher scores on internalising, externalising, and total behaviour problems compared with the controls.[27] By contrast, our study did not find evidence of a causal relationship between EP/ELBW birth and internalising and externalising behaviours, however, these disparities may be due in part to the different measures used, and that only 61% of children born EP/ELBW in our study had ITSEA data limiting the power of our study.

Social-emotional and behavioural difficulties identified at 2 years in the EP/ELBW children in the current study are potentially related to later behavioural outcomes. While there is evidence that some behavioural measures at 2-3 years are associated with specific social-emotional and behavioural outcomes at 5-6 years in a healthy birth cohort,[28] or children born

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very preterm,[29] further longitudinal research is warranted in the EP/ELBW population. In a longitudinal follow-up study of children born <26 weeks' gestation, parent-reported internalising behaviours at 2.5 years was associated with conduct problems at 11 years.[7] Including measures of behaviour/social-emotional development as part of routine follow-up for children born EP/ELBW may help identify potential issues earlier in childhood to target family-centred early intervention for those at greatest risk. A parent-report measure such as the ITSEA may be useful to identify those children who require closer monitoring of their behavioural development or warrant more detailed assessment, which may include face to face assessments. Early intervention has been demonstrated to reduce social-emotional problems in children born preterm,[30] and clinicians providing follow-up for children born EP/ELBW may require further training in assessment and intervention for those with social-emotional difficulties.

Our study has a number of strengths. It is a population-based cohort of all EP/ELBW live births in the state of Victoria, Australia, who were offered intensive care. The follow-up rate for the outcome assessment was high, which allows for inferences to be made regarding the causal effect of being born EP/ELBW on development. The 2-year follow-up included standardised assessments of neurodevelopment by assessors who were unaware of the child's medical history, thus decreasing bias. We included assessment of social-emotional and behavioural development, using a psychometrically sound measure. We used contemporaneous term control norms as previous studies have shown that the Bayley-III tends to underestimate delay in our local population.[15, 31]

There were also some limitations to the study. It is possible that there are unmeasured confounders in the relationship between EP/ELBW birth and developmental outcomes. There was a relatively low rate of completion of the ITSEA for the EP/ELBW group, possibly related to the lower rate of English-only speaking in that group, which reduced the power to find group differences in social-emotional development. Another limitation was that the assessments were administered in English which may have reduced the response rate for the ITSEA. Parental mental health is known to have an important influence on children's development,[32] and we acknowledge it as a mediating factor for child development at 2 years. Exploration of the role of mediating factors in the DAG, including parental mental health, is beyond the scope of the current study where we wanted to investigate the overall effect of being born EP/ELBW. Further research specifically examining the mediating effect of parental mental health, such as anxiety and depression, on development in this population is warranted. Future studies may also incorporate multi-source data, and include information from early childhood service providers in addition to parent-reported

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assessments such as the ITSEA. Longer term follow-up of the cohort into later childhood is warranted in order to ascertain the effect of EP/ELBW birth on important domains including executive function, academic achievement and higher-level language skills, as well as other outcomes such as ASD.

CONCLUSION

Our study has demonstrated strong evidence of a causal relationship between being born EP/ELBW and an adverse effect on cognitive, language and motor development at 2 years' corrected age, with higher rates of delay, as well as higher levels of dysregulation and poorer social-emotional competence in the EP/ELBW group compared with normal birthweight, term-born controls. Based on these findings we recommend that children born EP/ELBW require close monitoring across developmental domains, including that of social-emotional competence, in early childhood.

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ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ASD	Autism Spectrum Disorder
Bayley-III	Bayley Scales of Infant and Toddler Development, Third edition
CI	Confidence interval
DAG	Directed acyclic graph
EP	Extremely preterm
ELBW	Extremely low birthweight
ITSEA	Infant-Toddler Social and Emotional Assessment
OR	Odds ratio
SD	Standard deviation
VICS	Victorian Infant Collaborative Study

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STATEMENT OF CONFLICT OF INTEREST AND FUNDING

The authors have no conflict of interests to declare.

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Table 1. Participant characteristics for children seen at 2 years' corrected age

Participant Characteristics	EP/ELBW (n=205)	Term controls (n=201)
Antenatal corticosteroids	189 (92.2)	8 (4.0)
Multiple birth	61 (29.8)	4 (2.0)
Male	103 (50.2)	105 (52.2)
Gestation at birth in weeks, mean (SD)	26.3 (1.9)	39.1 (1.2)
Birthweight in grams, mean (SD)	834 (176)	3478 (434)
Birthweight z-score, mean (SD)	-0.48 (1.23)	0.40 (0.87)
Intraventricular haemorrhage grade III/IV	9 (4.4)	0 (0)
Cystic periventricular leucomalacia	3 (1.5)	0 (0)
Necrotising enterocolitis	23 (11.2)	0 (0)
Oxygen at 36 weeks	101 (49.3)	0 (0)
Postnatal corticosteroids	65 (31.7)	0 (0)
Retinopathy of prematurity (≥ stage 3 in at least one eye)	29 (14.1)	0 (0)
Surgery in the newborn period	50 (24.4)	0 (0)
Private health insurance	84 (41.0)	95 (47.3)
English-speaking only	131 (63.9)	148 (73.6)
Corrected age at follow-up in years, mean (SD)	2.1 (0.2)	2.1 (0.1)
Cerebral palsy	13 (6.4)	1 (0.5)
Blind	1[a] (0.5)	0 (0)
Deaf	3[a,b] (1.5)	1 (0.5)

Data are n (%) unless otherwise specified; EP/ELBW=extremely preterm/extremely low birthweight; SD=standard deviation

[a]one child with cerebral palsy was blind and deaf; [b]another child with cerebral palsy was deaf but not blind

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Table 2. Two-year outcomes contrasted between birth groups

	EP/ELBW (n=205)	Term controls (n=201)	Adjusted mean difference[#] (95% CI)	*p* value
Neurodevelopment (Bayley-III)				
Cognitive composite score	97.5 (15.8) n=197	109.0 (13.3) n=195	-10.6 (-13.8, -7.4)	<0.001
Language composite score	95.5 (19.1) n=164	112.9 (16.4) n=177	-17.3 (-21.6, -13.0)	<0.001
• Receptive language scaled score	9.6 (3.7) n=164	12.6 (3.2) n=177	-3.0 (-3.9, -2.2)	<0.001
• Expressive language scaled score	8.8 (3.2) n=164	11.8 (2.9) n=177	-2.9 (-3.7, -2.2)	<0.001
Motor composite score	98.7 (16.9) n=195	111.5 (14.3) n=195	-12.0 (-15.4, -8.6)	<0.001
• Fine motor scaled score	11.1 (3.6) n=195	13.4 (3.0) n=195	-2.1 (-2.8, -1.4)	<0.001
• Gross motor scaled score	8.5 (2.6) n=194	10.4 (2.6) n=195	-1.8 (-2.4, -1.3)	<0.001
Social-emotional development (Infant Toddler Social Emotional Assessment)				
Externalising t score	48.4 (8.7) n=125	47.2 (8.6) n=166	1.4 (-0.8, 3.7)	0.21
Internalising t score	48.3 (10.4) n=125	47.4 (9.7) n=167	1.5 (-1.3, 4.2)	0.29
Dysregulation t score	49.9 (10.4)	46.8 (8.5)	3.0 (0.5, 5.6)	0.02

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	n=124	n=167		
Competence t score	47.6 (12.9)	53.3 (9.5)	-6.7 (-9.8, -3.5)	<0.001
	n=125	n=166		

Data are mean (SD: standard deviation) unless specified; # Mean differences are adjusted for private health insurance, English only spoken at home and multiple pregnancy. EP/ELBW= extremely preterm/extremely low birthweight;

CI = confidence intervals

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Table 3. Developmental delay and "at-risk" social-emotional development contrasted between birth groups

	EP/ELBW (n=205)	Term controls (n=201)	Adjusted OR[#] (95% CI)	*p* value
Cognitive delay	100/199 (50.2)	40/195 (20.5)	3.7 (2.3, 6.0)	<0.001
Language delay	83/167 (49.7)	29/177 (16.4)	5.3 (3.1, 9.0)	<0.001
Receptive communication delay	76/164 (46.3)	32/177 (18.1)	4.5 (2.6, 7.8)	<0.001
Expressive communication delay	75/164 (45.7)	18/177 (10.2)	7.8 (4.2, 14.4)	<0.001
Motor delay	93/198 (47.0)	35/195 (18.0)	3.9 (2.3, 6.3)	<0.001
Fine motor delay	84/195 (43.1)	28/195 (14.4)	4.2 (2.6, 7.5)	<0.001
Gross motor delay	53/194 (27.3)	12/195 (6.2)	5.8 (2.9, 11.7)	<0.001
Infant Toddler Social Emotional Assessment ("at risk" cut-off scores)				
Externalising	6/125 (4.8)	6/166 (3.6)	2.0 (0.6, 6.7)	0.24
Internalising	9/125 (7.2)	7/167 (4.2)	2.3 (0.8, 6.8)	0.12
Dysregulation	10/124 (8.1)	4/167 (2.4)	3.1 (0.9, 11.0)	0.08
Competence	17/125 (13.6)	8/166 (4.8)	4.1 (1.6, 10.2)	0.003

Data are n (%); [#] Odds ratios adjusted for private health insurance, English only spoken at home and multiple pregnancy. EP/ELBW= extremely preterm/extremely low birthweight; OR = odds ratio; CI = confidence intervals

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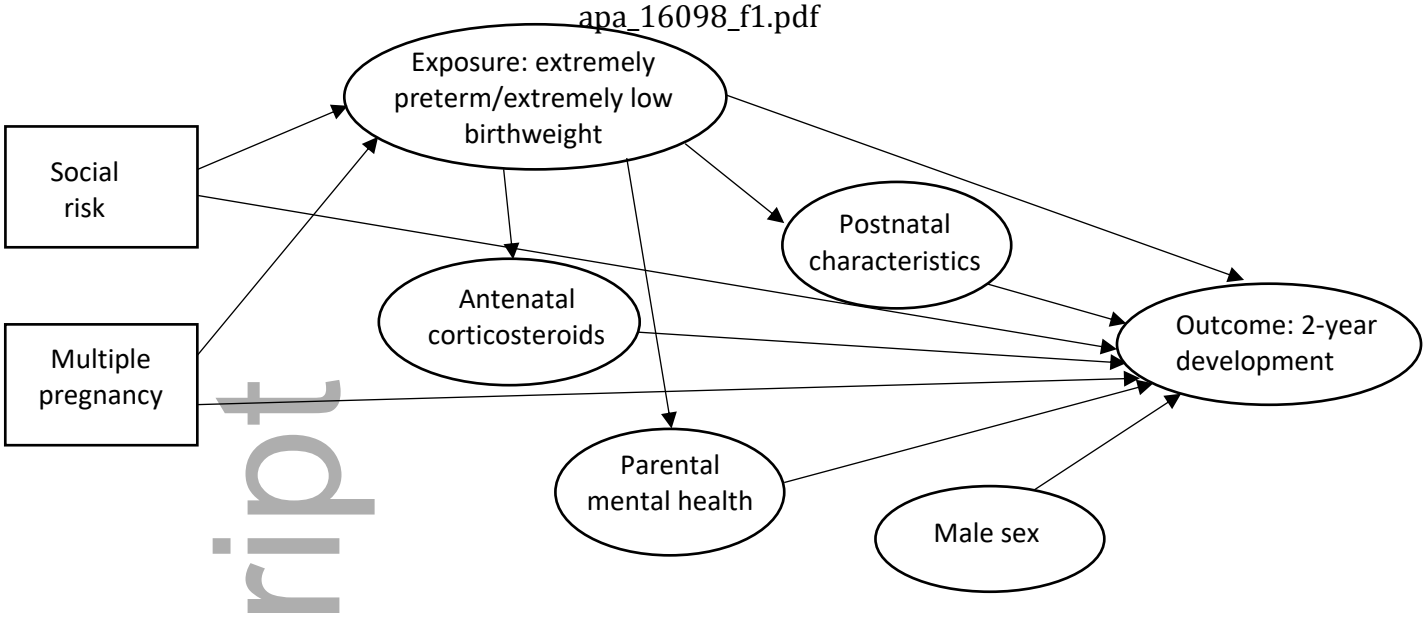


Figure 1. Directed acyclic graph for 2-year developmental outcomes depicting assumed causal relationship between variables

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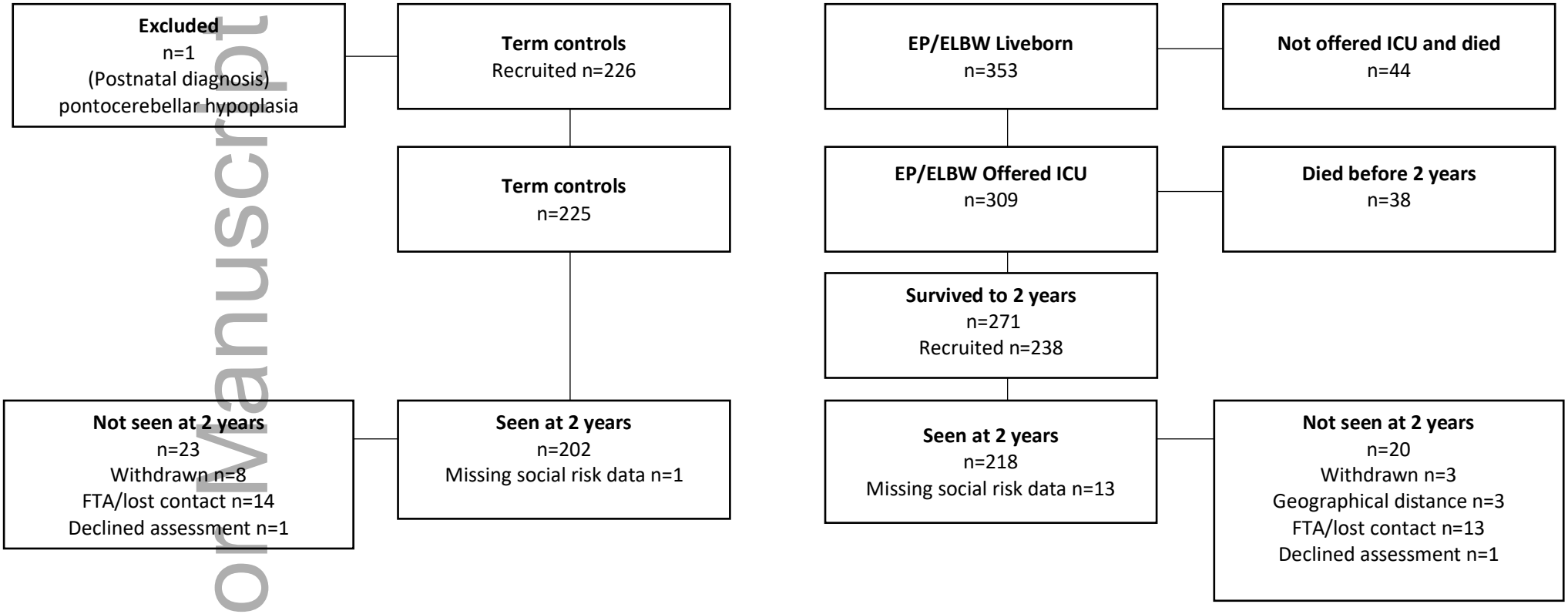
Social risk factors: language spoken at home (English only vs. other), private health insurance status

Postnatal characteristics: oxygen at 36 weeks, birthweight z scores, necrotising enterocolitis, surgery, postnatal corticosteroids, severe retinopathy of prematurity, brain injury: intraventricular haemorrhage (grade III/IV) or cystic periventricular leukomalacia

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Figure 2. VICS 2016 Participant Flowchart



Key: EP=extremely preterm <28 weeks' gestation; ELBW=extremely low birthweight (<1000g); FTA=failed to attend

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