Gestational Age, Ethnicity, and Associations with Developmental Disorders

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Abstract

Children born extremely preterm (<28 weeks gestation) are at risk of developmental disorders. There has been less research into outcomes of children born moderately preterm (32-33 weeks), late preterm (34–36 weeks), and early term (37-38 weeks). This means parents, clinicians, and educational professionals do not have access to accurate information about the likelihood of developmental disorders. Anticipating the disorders children are most at risk of could facilitate efficient diagnosis and service planning.

A systematic review showed that there was increased risk of most developmental disorders among moderately preterm children, but also late preterm and early term children, compared with term born children. There was little UK data on outcomes of children from minoritised ethnic groups born preterm. This informed two studies using Born in Bradford data. The first was the most comprehensive UK study of the full range of developmental disorders in relation to gestational age. Birth before full-term was associated with increased odds of developmental disorder which persisted after adjusting for covariates and in stratified analysis of Asian children; important since birth before full-term is more common among minoritised ethnic groups. The most common developmental disorder varied with ethnicity; compared to Asian children, White children had higher rates of autism spectrum disorder, but lower incidence of learning disabilities. Latent class analysis revealed most children (95.2%) had "typical development" with low risk of developmental disorders. The remainder were classified into: “Social, emotional, behavioural, and communication difficulties’’ (1.4%); “Educational difficulties” (2.6%); “Early developmental impairment, with physical and intellectual disabilities” (0.8%). The latter two groups were associated with birth before full-term.

Children with additive risk factors may benefit from additional follow-up. Children born late preterm and early term are at particular risk of educational difficulties (e.g. dyslexia and dyscalculia), reinforcing the need for better integration of health and education services.

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Author's Declaration

I declare that this thesis is a presentation of original work, and I am the sole author. This work has not previously been presented for a degree or other qualification at this University or elsewhere. All sources are acknowledged as references.

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- Developmental disorders in children born at 32-38 weeks gestation: a meta-analysis; British Association for Community Child Health (BACCH) Annual Scientific Meeting, Manchester, 12th September 2023

Chapter 1: Background

This thesis reports an investigation into developmental disorders amongst children born before full term. In this chapter, terminology is defined, the contextual background to the relationship between gestational age and developmental disorder is presented, and the aims, objectives, and structure of the thesis are outlined. The studies included in this thesis assess the prevalence and risk of developmental disorder amongst children born before full term, relative to those born at term; the factors associated with developmental disorders in children born before full term; and finally, how developmental disorders co-occur, and how this is related to gestational age.

1.1. Gestational age and preterm birth

Preterm birth is defined as birth before 37 weeks gestation following the onset of the last menstrual period, with the five week period between 37 and 41 weeks gestation being broadly classed as 'term' (Spong, 2013). Gestational age can be further divided into the following categories, according to how many weeks of the pregnancy are completed:

- <28 weeks: extremely preterm (Moutquin, 2003)
- 28 - 31 weeks: very preterm (Quigley, Poulsen, Boyle et al., 2012b)
- 32 - 33 weeks: moderately preterm (Boyle, Johnson, Manktelow et al., 2015)
- 34 - 36 weeks: late preterm (previously known as 'near term') (Woythaler, 2019; Boyle et al., 2015; Fleischman, Oinuma and Clark, 2010)
- 37 - 38 weeks: early term (Spong, 2013; Fleischman et al., 2010)
- 39 - 41: weeks: *full* term (Fleischman et al., 2010)
- ≥42 weeks: post term (Spong, 2013; Quigley et al., 2012b; Fleischman et al., 2010)

These definitions have been accepted by the World Health Organisation, but are not universally adopted, for example, babies less than *and including* 32 weeks gestation are sometimes referred to as 'very preterm' (World Health Organization, 2023; Larroque, 2004).

Previous research has focused on the outcomes of extremely preterm babies, who, as well as having a significant risk of mortality, also face an increased risk of developmental disorders, as discussed later (Johnson, Evans, Draper et al., 2015a; Boyle and Boyle, 2013; McGowan, Alderdice, Holmes et al., 2011). However, these children represent a small minority of the total number of live births every year, see Table 1.

Table 1 - Birth characteristics by gestational age in England and Wales: 2021 (Office for National Statistics, 2023)

Gestation age, completed weeks	**Gestational age group name**	**Number of live births**	**Percentage of total live births**
<28 weeks	Extremely preterm	2,874	0.5%
28 - 31 weeks	Very preterm	4,698	0.8%
32-33 weeks	Moderately preterm	5,881	0.9%
34 - 36 weeks	Late preterm	33,696	5.4%
37 - 38 weeks	Early term	151,552	24.3%
39 - 41 weeks	Full term	411,825	65.9%
≥ 42 weeks	Post term	11,478	1.8%
Gestation not stated or inconsistent with birthweight		2,158	0.3%
Total live births, all gestational ages		624,162	100%

The outcomes of children born between 32 – 38 weeks gestation, i.e., moderately preterm, late preterm, and early term are the focus of this thesis.

- Since the outcomes of children born 'early term' will be explored, as well as those born preterm, in this thesis children born '**less than *full* term**' will be used to mean any child born <39 weeks gestation.
- **Full term** will be used to refer to children born between 39-41 weeks, i.e., excluding children born **post term** (≥ 42 weeks), who, for different reasons, may also have an increased risk of developmental disorder (Mackay, Smith, Dobbie et al., 2010).

1.1.1. Measurement of gestational age

The exact date of conception is often unknown. Gestational age has historically been determined based on the first day of the woman's last menstrual period (LMP), but this has been found to be unreliable, especially as many women will not have a definitive menstrual history (Dudley, Kirwin, Dack et al., 2004; Campbell, Warsof, Little et al., 1985). Crown-rump length measurement by ultrasound, carried out at the end of the first trimester, can accurately determine gestational age to within 3 – 7 days (Callen and Norton, 2016). Therefore, in the UK it is recommended that ultrasound measurements of gestational age at the end of the first trimester (the 'dating' scan) should be used in preference to LMP (Dudley et al., 2004). Internationally this is often not done; there are large parts of the world where first trimester antenatal scanning is either not routinely recommended or not routinely carried out (Hunter, 2009). For example, in the USA, although a first trimester dating scan is recommended by the United States Institute of Medicine (Behrman, 2007), a key working group decided this was impractical and that the first scan could be carried out at the same time as the anatomy scan (18-20 weeks gestation) in cases where the menstrual history is clear (Spong, 2013).

1.1.2. Factors associated with birth before full term

There is wide variation internationally in the proportion of children born preterm; in 2020 the proportion of babies born preterm globally was 9.9% (9.0-11.0%), which has not changed substantially in the last ten years (Ohuma, Moller, Bradley et al., 2023); in England and Wales the figure is lower, 7.6% (Office for National Statistics, 2023), although this is higher than in some European countries; e.g. 5.5% in Sweden and 6.2% in Denmark (Norman, Padkær Petersen, Stensvold et al., 2023).

Understanding the history leading up to preterm delivery is important as it may have implications for the child's short and long-term outcomes. Preterm birth may occur spontaneously, or may be the result of obstetric intervention, either by caesarean or vaginally following induction of labour due to medical concerns about the mother or the fetus (Aughey, Jardine, Knight et al., 2023). The proportion of babies born preterm following iatrogenic delivery has been shown to vary between hospitals in England, more so than the proportion of spontaneous preterm births, perhaps because iatrogenic deliveries are more likely to be influenced by local medical practice and guidelines (Aughey et al., 2023). Potential factors associated with birth before full term are summarised in Table 2.

Table 2 - Risk factors for preterm birth

Medically indicated (iatrogenic) preterm delivery
Maternal • Pre-eclampsia • Medical acute illness or chronic conditions • Obstetric complication • Antepartum bleeding • Maternal age >35 years Fetal • Intrauterine growth restriction • Unstable fetal condition • Fetal anomaly • Multiple pregnancies
Spontaneous preterm delivery
With preterm premature rupture of the membranes (PPROM) • Infection • Uterine distension • Cervical anomalies • Social deprivation Without PPROM • Previous preterm birth • Low body mass index • Strenuous physical workload • Uterine anomalies • Psychological stress • Smoking or drug abuse • Maternal age <18 years

adapted from (Goldenberg, Culhane, Iams et al., 2008)

1.2. Developmental disorders

Child development can be defined as the "patterns of change over time which begin at conception and continue throughout the lifespan" and can be subdivided into different domains: physical, social, emotional, and cognitive (Keenan, 2016). Although each child will develop at a unique pace, there is a recognisable sequence to children's development and broadly accepted milestones which can be monitored. When a child does not reach a particular developmental milestone, or their acquisition of developmental skills is atypical, they should be assessed for the presence of a developmental disorder, defined as: "heterogeneous conditions that share a disturbance in the acquisition of basic developmental skills in a chronologically appropriate manner" (Shevell, 2010).

In the National Institute for Health and Care Excellence (NICE) guideline for developmental follow-up of children and young people born preterm, developmental disorders are defined as:

"A group of problems that become apparent during child development and often occur together. They are characterised by impairments of personal, social, academic, or occupational functioning, ranging from very specific limitations to global impairments of social skills or cognition, as measured by parent or teacher reports and surveillance tools. The term 'disorder' applies if the condition is severe, persistent and pervasive" (NICE, 2017b).

This definition, and the range of conditions considered in the NICE guideline, is used throughout this thesis. The NICE guideline is a widely used evidence-based document, which is recognised by a range of professionals involved in the care of children and young people, such as healthcare professionals, and those working in education and social care. The guideline includes a broad range of conditions, which reflects the reality that developmental disorders often overlap and co-occur (Shakeshaft, Heron, Blakey et al., 2023; Otterman, Koopman-Verhoeff, White et al., 2019; Thapar, Cooper and Rutter, 2017; Tonnsen, Boan, Bradley et al., 2016); a narrower focus would have given an incomplete picture of the experiences of those living with these disorders and would not have allowed comparison of risk and prevalence between conditions.

The specific developmental disorders that the NICE guidance states that children born preterm are at increased risk of are as follows:

1) Cerebral palsy
2) Motor function problems, including developmental coordination disorder (previously known as dyspraxia)
3) Learning disability (intellectual disability)
4) Special educational needs (SEN) and low educational attainment
5) Executive function problems
6) Speech, language, and communication disorders
7) Attention, impulsivity, and hyperactivity problems, and attention deficit hyperactivity disorder (ADHD)
8) Autism spectrum disorder (ASD)
9) Emotional and behavioural problems
10) Feeding problems
11) Sleep apnoea
12) Visual impairment
13) Hearing impairment
14) Developmental delay

A note on terminology

The disorders listed above are as they are named within the NICE guideline. These will largely be the terms used throughout this thesis, but there are problems with this terminology. The term 'autism spectrum disorder' (ASD) was introduced when the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) merged all of the diagnoses that were previously known as different pervasive developmental disorders (Oberman and Kaufmann, 2020). Some autistic people prefer the term 'autism spectrum condition' (ASC) to be used as a direct synonym for ASD, in order to convey that autism can come with strengths as well as difficulties (Lipinski, Blanke, Suenkel et al., 2019). Patient and public involvement and engagement work has also shown that in many cases the term 'autistic person' is preferred to 'person with autism', in order to reflect how autism is integral to a person's self, as opposed to a separate 'condition' (N8 Research Partnership, 2024). For consistency with the DSM-5 and with the International Classification of Diseases (ICD), eleventh edition, the term ASD will be used throughout this thesis.

Anecdotal evidence from informal discussions with families has suggested that some parents of children with developmental disorders prefer to use 'chance' or 'likelihood', as opposed to 'risk' as these words do not imply negativity, when discussing the probability of a disorder occurring. The term 'risk', particularly 'relative risk' and 'relative risk ratio' have specific meanings, and so need to be used at points in this thesis, but we acknowledge these families' view, and will aim to use 'likelihood' rather than risk where possible whilst maintaining accuracy.

1.2.1. Definition, diagnosis, and prevalence of individual developmental disorders

Brief descriptions or definitions of the individual disorders listed in the NICE guideline are summarised in Table 3, along with prevalence and typical diagnostic tools, however for most developmental disorders there is no definitive or diagnostic test (Price & Raffelsbauer, 2012).

Table 3 - Summary of the definitions, diagnostic tools, and prevalence of the developmental disorders

Definition	Diagnostic process/tool	Prevalence
Cerebral palsy (CP)		
A chronic disorder of movement and/or posture resulting from a non-progressive injury to the fetal or infant brain. CP may also affect perception, sensation, cognition, communication, and behaviour (Richards and Malouin, 2013). It can be classified according to the Gross Motor Function Classification System (GMFCS) (Rosenbaum, Palisano, Bartlett et al., 2008).	Clinical diagnosis, usually in conjunction with neuroimaging (Michael-Asalu, Taylor, Campbell et al., 2019)	0.3% in England between 2004-2014 for children and young people aged 0–25 years (Carter, Verity Bennett, Bethel et al., 2019).
Motor function problems, including, developmental coordination disorder (DCD)		
The NICE guideline for Developmental follow-up of children and young people born preterm refers to 'motor function problems', a very broad category of disorders, of which Developmental Co-ordination Disorder (DCD) is a specific type, which the guideline specifically mentions. The name DCD replaces the previous term 'dyspraxia'. DCD is an impairment in motor co-ordination, and by definition must interfere with activities of daily living or academic achievement in order to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (Lingam, Hunt, Golding et al., 2009)	Specific assessments can be carried out such as the Movement Assessment Battery for Children or the "Motor Skills screening Test" (Gibbs, Appleton and Appleton, 2007)	1.8% in England at a mean age of 7.5 years (Lingam et al., 2009). However, the children in this study likely represent more severe cases, with as many as 10% of children estimated to have mild symptoms of DCD (Gibbs et al., 2007).
Learning disability (intellectual disability)		

Definition	**Diagnostic process/tool**	**Prevalence**
In the UK, this refers to a deficit in cognitive ability, which affects daily life. To meet the ICD-10 criteria, the child's IQ score must be > 2 standard deviations below the mean (NICE, 2017b). Note that in the USA learning disability has a different meaning and refers to failure to acquire academic skills *not* related to cognitive ability (Johnson, 2017; Lagae, 2008). In the UK we would refer to this as a 'learning difficulty', such as dyslexia or dyscalculia (Robert Tasker, 2008), therefore the term 'intellectual disability' is less confusing for an international audience.	Psychological Assessment (Maulik, Mascarenhas, Mathers et al., 2011)	2.5% amongst children in England in 2014-15 (Public Health England, 2016)
Special Educational Needs and Disabilities (SEND)		
SEND is not a diagnosis in itself, rather it is an umbrella term used to refer to any child who requires additional support in education because of a learning difficulty or a disability. It is defined as any difficulty which necessitates special educational provision; a SEND requirement is anything which makes it harder for children to learn compared to other children the same age (Department for Education, 2014)). There are four broad categories of SEND: Communicating and interacting; Cognition and learning; Social, emotional, and mental health difficulties; Sensory and/or physical	Not applicable	4.0% of children in England have an EHCP, 12.6% have SEND but do not have an EHCP (Office for National Statistics, 2022).

Definition	Diagnostic process/tool	Prevalence
needs. Children who require more than SEND support are eligible for an EHCP following a statutory assessment (Department for Education, 2023). An EHCP specifies the additional support a child will require. They are multi-agency documents, largely written and enacted by Special Educational Needs Co-ordinators (SENDCOs) (Richards, 2021). Some studies and guidelines including NICE use the previous term Special Educational Needs (SEN).		
Executive function (executive control or cognitive control) problems		
Executive functions are a group of inter-related cognitive processes which help organise and regulate thoughts and subsequent actions. There are three core executive functions: 1) shifting between multiple tasks 2) updating informational content based on new incoming information 3) inhibiting automatic, or dominant responses (Miyake, Emerson and Friedman, 2000). Children with executive function problems may have issues with self-control, restlessness, aggression, abstract thinking, or cognitive planning and organisation (NICE, 2017b; Burgess, 2003; Brown, 2002).	The diagnosis is based on history and examination along with psychometric tests such as: working memory span (Diamond, 2013), the Wisconsin Card Sorting Task (Burgess, 2003), the Behavior Rating Inventory of Executive Function (BRIEF) (Sanz, Berl, Armour et al., 2017), and the Tower of Hanoi and London tasks (Miyake et al., 2000).	Abnormal scores on the BRIEF were found in 5-14% of children, depending on subdomain tested (Sanz et al., 2017)

Definition	Diagnostic process/tool	Prevalence
Speech, language, and communication disorders		
There are many types of speech, language, and communication disorder. Some children have a communication difficulty, but not a speech impairment, and other developmental disorders have a component of a speech, language, and communication disorder, for example ASD is defined in part by difficulty with communication (Baron-Cohen and Lombardo, 2017). Speech sound disorder (also known as a speech impairment) is one example of a Speech, language, and communication disorder and is defined as: “any combination of difficulties with perception, articulation/motor production, and/or phonological representation of speech segments (consonants and vowels), phonotactics(syllable and word shapes), and prosody (lexical and grammatical tones, rhythm, stress, and intonation) that may impact speech intelligibility and acceptability” (International Expert Panel on Multilingual Children's Speech, 2012).	Assessment by a speech and language therapist.	Speech sound disorder may affect up to 25% of preschool age children. This falls as children age; approximately 4% of 8 years old have a speech disorder (Wren, Pagnamenta, Peters et al., 2021).
Attention deficit hyperactivity disorder (ADHD)		

Definition	**Diagnostic process/tool**	**Prevalence**
Attention deficit hyperactivity disorder (ADHD) is characterised by pervasive excessive activity, impulsivity and inattention (NICE, 2018 ; Sayal, Prasad, Daley et al., 2018)	Diagnosis is based on history and examination and should only be made by a specialist psychiatrist, paediatrician or other healthcare professional with specific training and expertise in the diagnosis of ADHD (NICE, 2018).	Prevalence ranges from 1 – 9 % in childhood, depending on context and definition (NICE, 2018).
Autism spectrum disorder (ASD)		
Autism spectrum disorders are characterised by impairments in reciprocal social interaction and communication, in combination with rigid and repetitive behaviours and restricted interests. The term ASD is used to include four previous terms from the DSM-IV: • Autistic disorder (autism), • Asperger's disorder, • Childhood disintegrative disorder pervasive developmental disorder not otherwise specified (NICE, 2017a)	History and examination in conjunction with a specific autism assessment tool (NICE, 2017a).	Ranged from 0.7%- 1.8% in studies from the UK (Russell, Stapley, Newlove-Delgado et al., 2022; Roman-Urrestarazu, Van Kessel, Allison et al., 2021).
Feeding problems		
The NICE guideline for the developmental follow up of children born preterm refers to 'oro-motor feeding problems'. Feeding problems can have a diverse range of underlying causes and clinical presentations. They can result from a problem with, or lack of co-ordination of,	Assessment by multidisciplinary teams, for example paediatricians, speech and language therapist, occupational and physiotherapists. Barium swallow studies or a fibreoptic evaluation	Approximately 1% of children in the general population (Dodrill and Gosa, 2015)

Definition	Diagnostic process/tool	Prevalence
chewing, sucking, swallowing, respiratory endurance, and airway protection with overarching neurological control (Kamity, Kapavarapu and Chandel, 2021; NICE, 2017b; Dodrill and Gosa, 2015).	of swallowing (FEES) studies *may* be carried out (Kamity et al., 2021)	
Sleep problems, specifically sleep apnoea		
Sleep apnoea results from a partial or complete obstruction of the upper airway (most commonly by tonsil/adenoid hypertrophy) during sleep. This causes oxygen desaturation and hypercapnia, which eventually rouses the child, resulting in broken non-restorative sleep. (Li, Celestin and Lockey, 2016; Gozal, Tan and Kheirandish-Gozal, 2013)	Clinical diagnosis based on history and examination, confirmed by polysomnographic findings (Li et al., 2016).	Between 1%−5% in economically developed countries. Prevalence peaks between 2 – 8 years. (Gozal et al., 2013; Raynes-Greenow, Hadfield, Cistulli et al., 2012; Bixler, Vgontzas, Lin et al., 2009; Rosen, Larkin, Kirchner et al., 2003)
Visual Impairment		
Definitions vary globally but are usually based on the visual acuity in the better eye, therefore a child with unilateral VI (even if severe) will not be classified as visually impaired. In the UK the term sight impaired is commonly used in preference to visual impairment and has replaced the previous term 'partially sighted'. Severely sight impaired has replaced the term 'blind' in the UK (Solebo and Rahi, 2014).	Routine clinical surveillance or ophthalmic examination. (Rahi, Cumberland and Peckham, 2010)	0.2% of children are severely visually impaired in economically developed countries. (Teoh, Solebo and Rahi, 2017).

Definition	Diagnostic process/tool	Prevalence
Hearing Impairment		
Like visual impairment this is based on the 'better' ear. Disabling hearing impairment is defined by the World health organisation as the permanent pure-tone hearing threshold level of ≥ 31 dB averaged over the frequencies of 0.5, 1, 2, and 4 kHz (World Health Organization. Programme for the Prevention of and Hearing, 1997).	In the UK all newborns are offered evoked otoacoustic emission (OAE) testing within the first 4-5 weeks of birth. Additional tests can be carried out if there are hearing concerns later e.g., at 6-8 months, distraction tests, audiometry from 9 months. Neuroimaging may be done if a specific cause is suspected (Dimitrov and Gossman, 2023)	13.1% of children have bilateral hearing loss of at ≥ 15 dB. Self-reported hearing loss amongst children is lower, at 1.2% (Wang, Sung, Carew et al., 2019)
Developmental delay		
Significantly delayed milestones in one or more of the four child developmental domains: gross motor, fine motor, speech/communication and language, personal and social (Majnemer and Shevell, 1995). This means that what is initially diagnosed as a developmental delay may later be diagnosed as one of the other disorders above. The term "Early developmental impairment" is preferred by some, as "delay" may sometimes falsely imply a child will 'catch up' (McDonald and Rennie, 2011).	Clinical diagnosis: i.e., based on history and examination. Investigations may be useful in determining the underlying aetiology, but are not necessary to make the diagnosis (McDonald, 2006)	May affect between 5 – 10% of preschool children (Oberklaid and Efron, 2005; Majnemer and Shevell, 1995).

** Conditions listed in the order they appear in NICE guideline for the follow up of children born preterm (NICE, 2017b)*

1.3. Developmental disorders amongst children born before full term

There is a known association between preterm birth and developmental disorders, but the majority of research thus far has focussed on babies born ≤32 weeks, including the large cohort studies Epicure, Epicure 2, EPIPAGE (Étude épidémiologique sur les petits âges gestationnels) and EPIPAGE 2 (Marlow, Wolke, Bracewell et al., 2005; Larroque, 2004). These studies have revealed that developmental disorders affect between 35-50% of surviving children who are born very preterm (Luu, Mian and Nuyt, 2017). As well as tending to focus on babies born ≤32 weeks, outcomes are often only measured up until 2 years of age (Johnson et al., 2015a; Kugelman and Colin, 2013). A further issue with existing work exploring developmental outcomes of children born before full term, is that study populations are often dichotomised into 'preterm' (<37 weeks) and 'term' (>37 weeks) (Odd, Evans and Emond, 2019), thus limiting the investigation into the relationship with the full spectrum of gestational age. In fact, there is emerging evidence suggesting any birth before full term, including at 37-38 weeks, may also be associated with developmental disorders, therefore children born 37-38 weeks should not be included within "term" comparison groups (Vohr, 2013; Quigley et al., 2012b).

1.3.1. Conceptual Framework

There are multiple reasons why children born before full term might be at increased risk of developmental disorders, summarised in Figure 1 and discussed below.

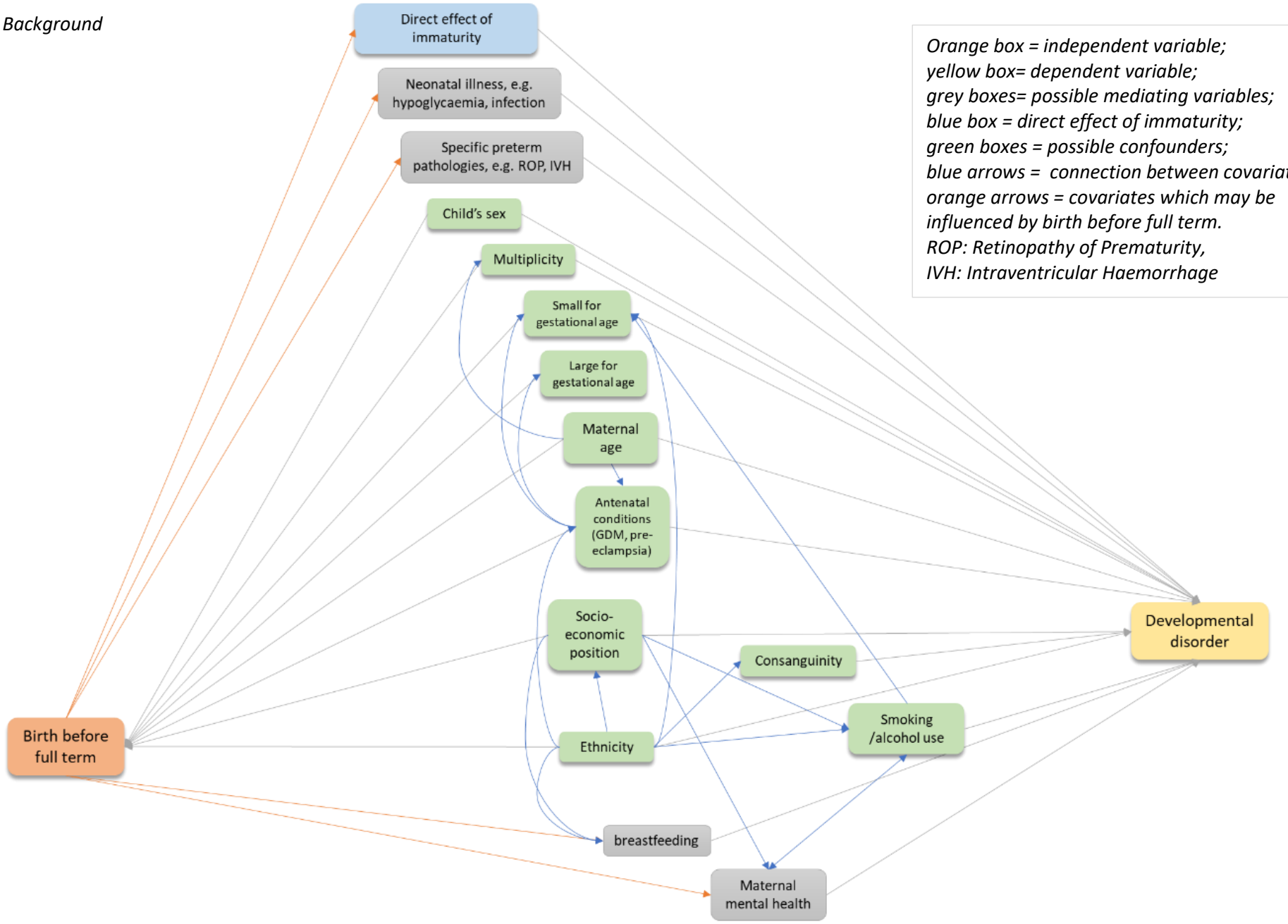


Figure 1 - Figurative representation showing possible associations between exposure (birth before full term), outcome (developmental disorder) and covariates

1.3.1.1. Direct effect of immaturity

Whilst a baby born just a few weeks early may appear well grown, their brain maturation is markedly different to that of a full term child: at 34 weeks and at 38 weeks the brain weighs 65% and 90% of its full term equivalent weight respectively (Nielsen, Pedersen, Milidou et al., 2019; Kapellou, Counsell, Kennea et al., 2006; Kinney, 2006). It is possible that birth at this stage may disrupt the normal development of neural connections and brain maturation, resulting in developmental disorder, even in the absence of demonstrable structural brain abnormalities (Chan, Leong, Malouf et al., 2016; Kugelman and Colin, 2013).

1.3.1.2. Neonatal illness

Children born before full term are more likely to have medical complications in the neonatal period, such as jaundice, hypoglycaemia, respiratory distress, and temperature instability (Chan et al., 2016). In some cases, these can lead directly to a developmental disorder.

1.3.1.3. Specific preterm pathologies

Some children born preterm, particularly those with very low birth weight (<1.5kg) or born very preterm, are at risk of specific pathologies of prematurity. The majority of children born moderately preterm, late preterm, or early term, (who are the focus of this thesis) are at low risk of these conditions, but since they are referenced later, they are discussed here for completion.

Retinopathy of prematurity (ROP)

ROP is a consequence of the delivery of excessive supplemental oxygen, which results in abnormal vascularisation of the retina; if severe and left untreated can cause retinal detachment and blindness (Hellström, Smith and Dammann, 2013). Nationally, ROP is the cause of 4% of cases of severe visual impairment (Teoh, Solebo and Rahi, 2021). All babies at risk of ROP (<1501 grams or <31 weeks gestation) should have screening, in order that it can be detected and treated promptly, as per Royal College of Paediatrics and Child Health (RCPCH) guidelines (Royal College of Paediatrics and Child Health RCPCH, 2022).

Intraventricular Haemorrhage (IVH)

IVH is the most common type of intracranial haemorrhage in the preterm infant (Volpe, 1989). It is caused by fluctuant cerebral blood flow and the fragility of premature babies' germinal matrix vasculature, resulting in bleeding into the lateral ventricles inside the brain. If an IVH occurs, it usually happens within the first 3 days of life (Hand, Shellhaas, Milla et al., 2020; Ballabh, 2014). A

large IVH can cause an acute deterioration as well as affecting longer term outcomes: IVH is associated with CP, cognitive impairment, blindness and hearing loss (Bolisetty, Dhawan, Abdel-Latif et al., 2014). IVHs are screened for and monitored using cranial ultrasound (Bolisetty et al., 2014). In the UK there is no national guideline, but in Yorkshire all babies born <32 weeks or with a birth weight of <1500 grams are routinely screened for intracranial anomalies such as IVH with cranial ultrasound (Shetty, 2021).

Periventricular leukomalacia

Periventricular leukomalacia (PVL) is a characteristic pattern of necrosis within the brain's white matter which is associated with prematurity (Larroque, Marret, Ancel et al., 2003). PVL may be the result of an earlier IVH, or can result from an episode of infection, hypotension, or ischaemia (Volpe, 1989). PVL is associated with worse developmental outcomes, and conditions such as visual loss and cerebral palsy; classically spastic diplegia (Bolisetty et al., 2014; Owens, 2005).

1.3.1.4. Child's sex

Boys are more likely to be born preterm than girls (Ferrero, Larson, Jacobsson et al., 2016). The majority of developmental disorders are more common (or diagnosed more often) amongst boys than girls (Atkinson, Hill, Pettinger et al., 2022; Donald, Wedderburn, Barnett et al., 2019; Russell, Rodgers, Ukoumunne et al., 2014).

1.3.1.5. Multiplicity

Multiplicity is a risk factor for preterm birth (Harrison and Goldenberg, 2016). Cerebral palsy is more common in twins than in singletons, even when accounting for gestational age (Perra, Rankin, Platt et al., 2021).

1.3.1.6. Maternal age

Pregnancy at either extreme of maternal age is associated with increased risk of preterm birth (Harrison & Goldenberg, 2016). Advanced maternal age is an established risk factor for genetic conditions such as trisomy 21 and has been shown to be associated with increased risk of developmental disorders such as ASD (Sandin et al, 2012). However, starting a family at a later stage is also associated with higher income and increased educational attainment (Tearne, 2015).

1.3.1.7. Antenatal conditions

Birth before full term is often the result of maternal ill health (such as pre-eclampsia, infection, gestational diabetes) and a resulting sub-optimal intrauterine environment (see Table 2). Pre-eclampsia is associated with increased risk of small for gestational age (SGA) (Shen, Smith, Rodger et al., 2017); gestational diabetes mellitus (GDM) is associated with large for gestational age (LGA) (Karkia, Giacchino, Hii et al., 2024); both are associated with prematurity. It is possible that these antenatal issues are the underlying cause for the increased risk and prevalence of developmental disorders, as opposed to the prematurity *per se* (Nielsen et al., 2019; Vohr, 2013) (Kugelman and Colin, 2013). Pre-eclampsia and diabetes during pregnancy have been shown to be associated with increased risk of developmental disorders including ADHD, cognitive impairment, and behavioural problems (Kong et al, 2022; Nogueira Avelar et al, 2021)

1.3.1.8. Socio-economic deprivation

Socio-economic deprivation is associated with an increased risk of preterm birth, explained in part by dietary insufficiency and smoking (Smith, Draper, Evans et al., 2015; Bonet, Smith, Pilkington et al., 2013; Taylor-Robinson, Agarwal, Diggle et al., 2011). Socio-economic deprivation is also associated with increased prevalence of developmental disorders such as motor delay, language impairment, cognitive impairment, and ADHD (Maalouf, Fearon, Lipa et al., 2021; Johnson et al., 2015a; Richards, Chapple-McGruder, Williams et al., 2015; Lindström, Lindblad and Hjern, 2011; McPhillips and Jordan-Black, 2007). Likewise low levels of maternal education are associated with both higher risk of preterm birth (Ruiz et al, 2015) and increased risk of developmental impairment (Atkinson et al, 2022; Donald et al, 2019). The connection between lower socio-economic position and developmental disorders does not fully explain the association between birth before full term and developmental disorder; it can still be demonstrated in studies using sibling control models (Yin, Döring, Persson et al., 2022; Heuvelman, Abel, Wicks et al., 2018).

1.3.1.9. Ethnicity

Studies from the USA have shown that Hispanic women, Black women, and native American women have higher prevalences of pregnancy related complications such as pre-eclampsia and gestational diabetes and are also more likely to be older and multiparous during pregnancy; which in turn increases risk of adverse pregnancy outcomes, including preterm birth (Johnson and Louis, 2022; Bornstein, Eliner, Chervenak et al., 2020). Indeed, compared to White women, Black

women are 2.5 times more likely to give birth prematurely, and since 1990, these disparities have grown (Oliveira, Araújo, Oliveira et al., 2018). Not only does the proportion of preterm babies born vary by ethnicity, but there are also ethnic disparities in neonatal morbidity experienced by preterm babies; with Black and Hispanic babies experiencing higher risk of retinopathy of prematurity (ROP), intraventricular haemorrhage, necrotising enterocolitis, and bronchopulmonary dysplasia, and Asian babies having higher rates of ROP, compared to White babies (Janevic, Zeitlin, Auger et al., 2018). There may be some genetic component to the increased risk of pregnancy complications and therefore adverse pregnancy outcomes (including preterm birth), but socio-economic deprivation, discrimination and structural racism likely also play a part (Van Daalen, Kaiser, Kebede et al., 2022; Bornstein et al., 2020).

Local context is important and caution should be applied when extrapolating research findings internationally, even between economically developed countries, due to differences in terminology, population characteristics, health and education services, and background rates of disorders (Global Research on Developmental Disabilities Collaborators, 2018). In England and Wales, the risk of preterm birth is also markedly different between ethnicities, which is not fully explained by socio-demographic characteristics (Office for National Statistics, 2023; Li, Quigley, Macfarlane et al., 2019). The risk is highest amongst Black women, although recently the largest proportional increase of preterm births was amongst Asian women (Office for National Statistics, 2023; Li et al., 2019).

UK data has shown that South Asian women have a higher risk of gestational diabetes and compared to White women, tend to deliver babies with greater adiposity (Arechvo, Voicu, Gil et al., 2022; Farrar, Fairley, Santorelli et al., 2015). International data shows that the risk is particularly high amongst South Asian women who have migrated to, as opposed to being born in, a western country (Yuen and Wong, 2015). There is also an association between SGA and ethnicity; White babies weigh on average 200-300g more at delivery compared to UK-born South Asian babies, which may be the result of lower socio-economic position (SEP) and a resultant suboptimal intrauterine environment, i.e. it is not necessarily normal physiology related to ethnic difference (Gardosi, Francis, Turner et al., 2018; Norris, Johnson, Farrar et al., 2015; Seaton, Yadav, Field et al., 2011; Kelly, Panico, Bartley et al., 2009; Kierans, Joseph, Luo et al., 2008). Sadly, it is likely that there is an element to which discrimination plays a role in differing outcomes: a systematic review mainly including participants from the USA showed that participant reported racial discrimination increased the odds of preterm birth (Van Daalen et al., 2022).

Given the increased prevalence of pregnancy complications and increasing risk of preterm birth amongst Asian women, understanding the risks faced by children born following this is important. The NICE guideline for the developmental follow up of children born preterm states that being from a "black, Asian or other minority ethnic group" is an independent risk factor for developmental delay (NICE, 2017b). However, most research from the UK exploring developmental outcomes of children born before full term is based on data where >70% of the participants were White (Alterman, Johnson, Carson et al., 2022; Alterman, Johnson, Carson et al., 2021; Odd et al., 2019; Cronin, Segurado, McAuliffe et al., 2016; Guy, Seaton, Boyle et al., 2015; Johnson et al., 2015a; Johnson, Matthews, Draper et al., 2015c; Chan and Quigley, 2014; Odd, Emond, Whitelaw et al., 2012). Whilst this is representative of the UK population, most of these cohorts contain under 20,000 children in total, thus since the majority are White and born at term, the conclusions which can confidently be drawn about the outcomes of children from minoritised ethnic groups who have been born before full term are limited; more research from the UK is required.

1.3.1.10. Consanguinity

The prevalence of consanguinity varies with ethnicity, and whilst it is unusual in White British families, over 75% of British people with Pakistani heritage are married to someone to whom they are genetically related (Khan, Benson, MacLeod et al., 2010a). Consanguinity is associated with increased child mortality, due to the increased risk of autosomal recessive disorders (Khan et al., 2010a). Consanguinity is also a risk factor for developmental disorders including hearing impairment, speech and language disorders, learning disability and hyperactivity (Small, Kelly, Malawski et al., 2024; Abbas and Yunis, 2014).

1.3.1.11. Maternal smoking and alcohol consumption in pregnancy

Maternal smoking is associated with increased risk of preterm birth (Vogel, Chawanpaiboon, Moller et al., 2018; Harrison and Goldenberg, 2016). Some studies have shown that children who had developmental disorders (specifically speech and language disorders, developmental coordination disorder and educational difficulties) were more likely to have had mothers who smoked in pregnancy (Arrhenius, Sariaslan, Suominen et al., 2021). However, this association was not significant in a sibling control model and other large studies have found no link between ASD

and ADHD with maternal smoking (Kalkbrenner, Meier, Madley-Dowd et al., 2020; Kalkbrenner, Braun, Durkin et al., 2012).

1.3.1.12. Breastfeeding

Breastfeeding has been shown to be associated with lower prevalence of behavioural problems (Heikkilä, Sacker, Kelly et al., 2011) and improved cognitive scores, which was reduced but not eliminated after adjusting for socio-economic position (SEP) (Pereyra-Elías, Quigley and Carson, 2022). Early term and late preterm children may be more likely to have shortened breastfeeding duration (Nicole M. Hackman, 2016).

1.3.1.13. Maternal mental health

Maternal mental health can impact child development; maternal depression is considered a risk factor for development of ADHD symptoms as well as impaired cognitive, social and emotional development (Stein, Pearson, Goodman et al., 2014; Bernard-Bonnin, 2004). Parents of children who have been born preterm are at risk of mental health problems: admission to the neonatal unit has been shown to be associated with parental acute stress disorder and post-traumatic stress disorder (Lefkowitz, Baxt and Evans, 2010). After the neonatal period, children born late preterm have been shown to be 2-3 times more likely to attend the emergency department or be admitted to hospital (Vohr, 2013; Baron, Litman, Ahronovich et al., 2012). The increased medical needs of children born before full term have an impact on both the child, and family. Parents of late preterm infants have been shown to have high emotional distress and anxiety levels (Vohr, 2013; Brandon, Tully, Silva et al., 2011).

1.3.2. Developmental follow-up of children born preterm

Delayed diagnosis of developmental disorders may lead to missed opportunities for early intervention, as well as causing distress to families and impacting upon their wellbeing (Lipkin, Macias, Norwood et al., 2020; Sahli, 2019; Mitchell and Holdt, 2014; Baird, McConachie and Scrutton, 2000). Likewise, late instigation of educational support can compound impaired learning, resulting in disengagement from school (Hughes, Foley, White et al., 2018). Early intervention has not only shown to be clinically effective, it is also cost effective (Jacobson, Mulick

and Green, 1998). Anticipating the challenges children are likely to face could assist prompt identification of needs, facilitating improved health and well-being (Lipkin et al., 2020).

In view of the importance of prompt diagnosis and intervention, as well as the known association between prematurity and developmental disorders it is recommended that children born <30 weeks are provided with enhanced developmental surveillance up to 2 years of age (NICE, 2017b). If parents or carers are concerned about their child's development and they are not under routine follow up they are advised to advice from their general practitioner (GP) or health visitor (NICE, 2017b), however, this requires a baseline knowledge of typical development as well as the ability and desire to access medical advice, which may be influenced by parents' social, cultural, or ethnic background, thus potentially exacerbating health inequalities (Lindquist, Kurinczuk, Redshaw et al., 2015; Dixon-Woods, Cavers, Agarwal et al., 2006; Scheppers, Van Dongen, Dekker et al., 2006; Szczepura, 2005).

1.4. Chapter summary

Children born extremely preterm are at increased risk of developmental disorders. This risk may extend to children born closer to their due date, but this has not been definitively established. Late preterm and early term birth are common and therefore the impact of an increased risk of developmental disorders in these groups at a population level could be substantial.

Many factors are associated with both birth before full term and the likelihood of developmental disorders. Previous research has tended to explore only one or two developmental disorders, as opposed to comprehensively investigating all developmental outcomes

Thus, the epidemiology of developmental disorders across the population of children born 32-38 weeks is not currently known. Filling this evidence gap is vital in order that:

- paediatricians can give evidence-based information to families
- the possibility of focussed follow up for subgroups of children born 32-38 weeks can be considered
- parents and professionals can be more aware of developmental risks, which could improve early identification and opportunities for intervention
- obstetricians can more fully evaluate the risk and benefits of timing of deliveries
- opportunities for co-operation with other sectors such as education can be maximised

1.5. Thesis aims and objectives

This thesis has four aims:

- To investigate the prevalence and risk of developmental disorders in children born before full term compared to those born at full term
- To determine the cumulative incidence and incidence rates of developmental disorders according to gestational age
- To explore profiles of developmental disorders
- To examine which factors, particularly ethnicity, are associated with the incidence and profiles of developmental disorder

The following objectives were designed to achieve these aims:

1. To conduct a systematic review and meta-analyses to determine the risk and prevalence of developmental disorders amongst children born between 32-38 weeks compared to children born at term.
2. To develop a list of clinical codes for primary and secondary care which correspond to the signs, symptoms, and diagnosis of the developmental disorders listed in the NICE guideline for developmental follow-up of children and young people born preterm (NICE, 2017b)
3. To determine the cumulative incidence and incidence rates of any developmental disorder, and of individual developmental disorders, in the Born in Bradford cohort
4. To explore how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity
5. To investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models
6. To carry out a latent class analysis to identify profiles of developmental outcomes
7. To determine which factors are associated with different profiles of developmental disorders

1.6. Thesis structure

This thesis is formed of seven chapters (Figure 2). Following this introductory chapter, the second chapter is a systematic review and meta-analysis of the risk and prevalence of developmental disorder amongst children born between 32-38 weeks gestation compared to children born at term. Chapter three describes the methods for the secondary data analysis using Born in Bradford data. Chapters four, five, and six present results of the secondary data analysis: chapter four presents the cumulative incidence and incidence rate of developmental disorders within the BiB cohort; chapter five presents the univariable and multivariable statistical modelling; chapter six presents the results of a latent class analysis, and how the profiles identified are associated with gestational age. The last chapter provides a summary, analysis, and conclusion to these results, with an emphasis on practical consequences for research as well as health policy and practice.

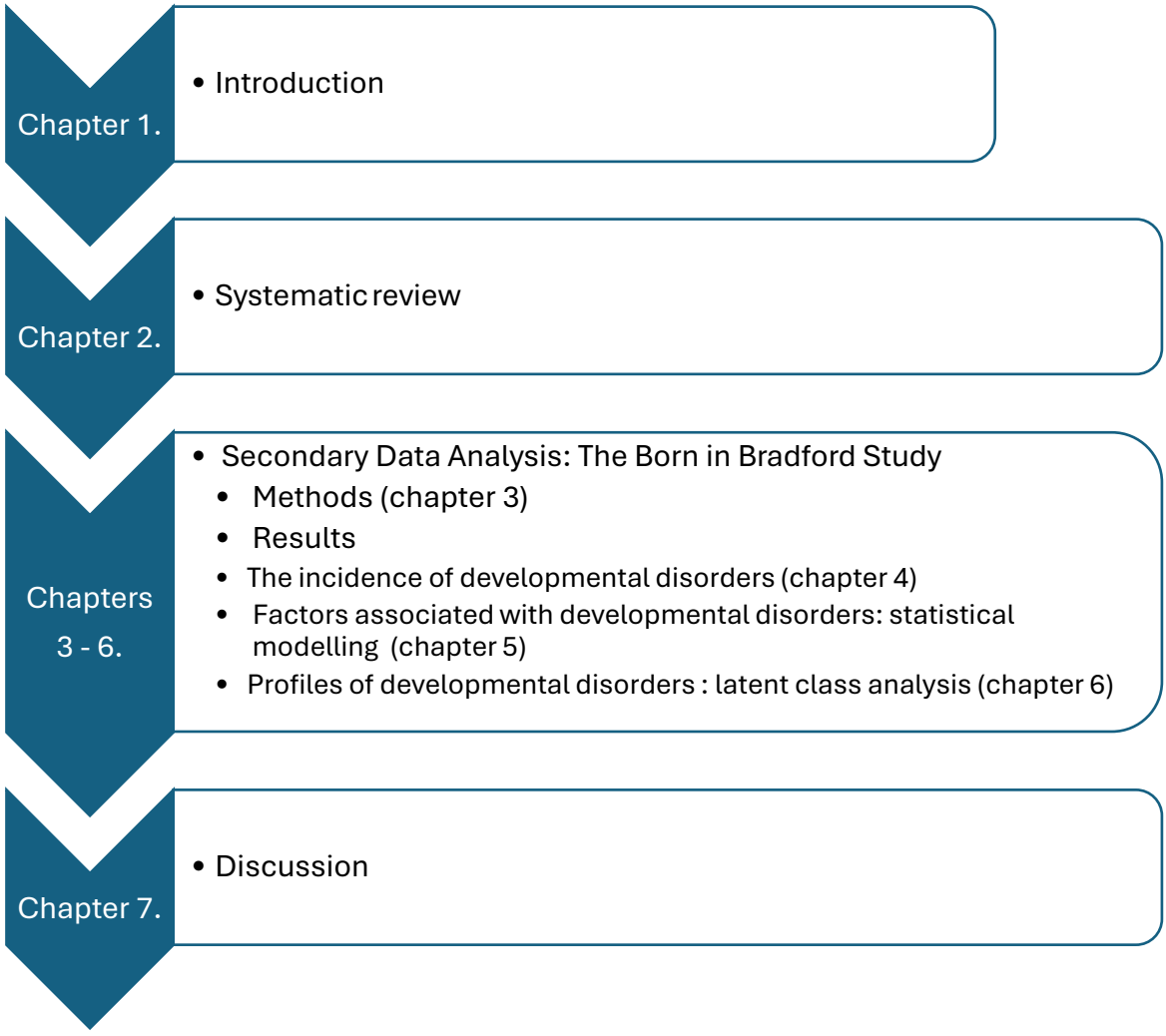


Figure 2 - Thesis structure

Chapter 2: Birth before full term and developmental disorder: a systematic review and meta-analysis

2.1. Introduction

This chapter describes the research conducted to fulfil the first objective of this thesis:

1. To conduct a systematic review and meta-analyses to determine the risk and prevalence of developmental disorders amongst children born between 32-38 weeks compared to children born at term.

The systematic review described in this chapter was published in *Pediatrics* on 10th November 2023 (Pettinger, Copper, Boyle et al., 2023). In the published study the number of included studies was reduced (to 76) for simplicity, to include only studies which were meta-analysed. Here, all eligible studies are included and summarised.

The rationale for further investigation into the developmental outcomes of children born between 32 - 38 weeks gestation was described in Chapter 1 – Background. This is the first systematic review and meta-analysis with the aim of determining the prevalence and risk relative to term born children of a full range of developmental disorders amongst children born moderately preterm, late preterm, and early term. Whilst there have been a few systematic reviews exploring *some* aspects of this question (e.g., (Teune, Bakhuizen, Bannerman et al., 2011)), none answered it in full, for example only considering moderate or late preterm children, or only exploring one type of developmental disorder. Therefore, an umbrella review was not possible, rather a new systematic review was felt to be the best way to answer the question from the available literature in the most thorough, least biased way (Grant and Booth, 2009).

2.2. Methods

The population of interest is children aged 2 – 17 years. A minimum age of two was felt to be important to avoid inclusion of children who have a transient developmental delay which is unlikely to result in a formal diagnosis at an older age. Earlier diagnosis of CP for example may represent a misdiagnosis (Spittle and Orton, 2014). In order to be included, children had to be born after 1996. This is because the administration of antenatal steroids to women with threatened preterm birth became routine practice in 1996 following publication of a Cochrane review (Lawn, Davidge, Paul et al., 2013), which had a major impact on mortality and morbidity. The exposure was birth before full term, specifically between 32+0 to 38+6 weeks gestation, compared to children born at term (≥37 weeks) or full term (39-41 weeks).

The outcome of interest was developmental disorder, as defined by The National Institute for Health and Care Excellence, as discussed in chapter 1 (NICE, 2017b). As well as searching for developmental disorder as a broad term, individual disorders were sought, as many studies only reported a single outcome. The search was designed to find all the developmental disorders mentioned in the NICE guideline, that is:

- Cerebral palsy
- Motor function problems, including developmental coordination disorder (previously known as dyspraxia)
- Learning disability (intellectual disability)
- Special educational needs (SEN), now referred to as special educational needs and disabilities (SEND), and low educational attainment
- Executive function problems
- Speech, language, and communication disorders
- Attention, impulsivity, and hyperactivity problems, and attention deficit hyperactivity disorder (ADHD)
- Autism spectrum disorder (ASD)
- Emotional and behavioural problems
- Feeding problems
- Sleep apnoea
- Visual Impairment
- Hearing Impairment
- Developmental delay

In order to provide adequate detail to allow repetition of the study, the protocol was developed as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P) and reported according to the PRISMA guidelines (Moher, Shamseer, Clarke et al., 2015).

PROSPERO, the International prospective register of systematic reviews, was reviewed on February 1st, 2022, for protocols with similar topics, but none with substantial overlap were found (CRD, 2022). Prior to initiating the review, the protocol was registered on PROSPERO (CRD42021298773), and is available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021298773). A copy of the protocol can be found in Appendix 2.1. Systematic review protocol. During the course of the review five minor changes were made to the protocol which were also updated in PROSPERO.

1. Non-English language studies were excluded. Whilst it was initially felt it might be possible to include these, it became too difficult to accurately extract data.
2. Excluded outcomes measured before the child is 2 years old. This was an omission on the first iteration of the protocol.
3. Excluded studies where ANY of the children were born pre 32 weeks, unless the data specifically from children born 32-38 weeks could be extracted. This was unclear on the protocol initially. It was felt that including any children who were more preterm than the specific group of interest could skew the results. This supersedes the previous exclusion criteria: "Studies where >10% of the study population were born <32 weeks gestation or the mean gestational age of participants is <32 weeks".
4. "The mean gestational age of the exposed group must be known" – this should have read: "The mean gestational age *or gestation age range* of the exposed group must be known".
5. "Included at least one neurodevelopmental disorder (or special educational need) as an outcome by a standardised test, physician diagnosis" should have read: "included at least one neurodevelopmental disorder (or special educational need) as an outcome by a standardised test, physician diagnosis or a validated questionnaire."

2.2.1. Search strategy

The electronic databases Medline, Embase, Psychinfo and cumulative index of nursing and allied health (CINAHL) were searched on 10th February 2022, identifying studies published from 1st January 1996 onwards. The searches were updated on 22nd November 2022, apart from the

Google scholar search, which had not yielded any additional papers when the searches were first undertaken. When designing my search strategy, advice was sought from the University of York Health Sciences information specialist David Brown.

Studies had to include both preterm or early term birth and developmental disorder concepts. Multiple terms were included in the search strategy in an attempt to exclude irrelevant studies. The search terms can be found in Appendix 2.2. Systematic review search terms.

Grey Literature

A Google scholar search was carried out on 14th February 2022. Initially the advanced search feature of Google Scholar was used, but the resulting studies were not relevant. Therefore, a basic search was performed using the question: *"What is the risk of neurodevelopmental disorder in children born between 32-38 weeks gestation?"*. The top 50 results were exported to Endnote, and along with the results from the electronic databases, sorted into folders according to where the reference had been identified. An initial de-duplication process in Endnote was undertaken when the authors and titles matched. Then the references were uploaded from the Endnote library into Covidence (https://www.covidence.org/).

Reference Lists

The reference lists of all included articles were searched for additional relevant articles to include which yielded an additional 15 further studies.

2.2.2. Study selection

The title and abstracts of all the identified from the search were screened by the primary reviewer (KP). As planned in the protocol, 20% of the screening was also carried out (independently) by a second reviewer (CC). Any disagreements were resolved by discussion. Agreement was assessed using Cohen's kappa statistic, generated by Covidence. The process was replicated for the full text screening, with KP screening all the studies and CC screening 20% of the studies independently. Where key data was missing the authors were contacted once by email; if no response was received the study was excluded from the meta-analysis.

2.2.3. Data extraction

Data was extracted by KP using a data extraction form which can be found in Appendix 2.3. Data extraction form. The data extraction form was piloted on five studies initially. Key study characteristics to extract included:

- Children's age at assessment
- Number of participants enrolled, and number included in analysis
- Definition of the outcome used
- Measurement tool used
- Country of study
- Recruitment strategy
- Ethnicity and sex of participants
- Exclusion and inclusion criteria.

In order to calculate the relative risk and prevalence for studies reporting binary outcomes the number of participants with and without developmental disorder in each gestational age group was recorded. In studies reporting continuous outcome the mean score, standard deviation, and number in each group was recorded. Where this was unavailable the standard deviation was calculated using confidence intervals or standard errors: (Higgins JPT, 2023)

$$SD = SE \times \sqrt{N}$$

$$SD = \sqrt{N} \times (\text{upper limit CI} - \text{lower limit CI})/3.92$$

SD: standard deviation, SE: standard error, N: sample size, CI: confidence intervals

If only pre calculated effect sizes with confidence intervals were presented, these were added into the meta-analysis manually. The second reviewer (CC) checked the accuracy of the data extraction on a sample of 20% of the included studies.

2.2.4. Risk of bias assessment

The Newcastle-Ottawa scale for cohort and case control studies was used to assess the quality of the included studies (Figure 3). It is a validated tool and simple to use. There are three domains: selection, comparability, and exposure. The total scores range from 0 – 9 and can be categorised into poor quality (0–2), fair quality (3-5), good/high quality (6-9) (Wells, 2021). The questions are as follows. One star equals one point. Questions 8 and 9 do not apply to cross sectional studies.

Section 1 – Selection

1) Representativeness of the exposed cohort:
a) truly representative of the average exposed individual in the community *
b) somewhat representative of the average exposed individual in the community *
c) selected group of users e.g., nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort:
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
a) secure record *
b) structured interview *
c) written self-report
d) no description

4) Demonstration that outcome of interest was not present at start of study
a) yes *
b) no

Section 2 – Comparability

1) Comparability of cohorts on the basis of the design or analysis
a) study controls for sex *
b) study controls for parental education/socio-economic status*

Section 3 – Outcome

1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self-report
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) *
b) no

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost: ≥70 % follow up, or description provided of those lost *
c) follow up rate < 70 % (select an adequate %) and no description of those lost
d) no statement

Figure 3 - The Newcastle-Ottawa scale for cohort and case control studies

2.2.5. Meta-analyses

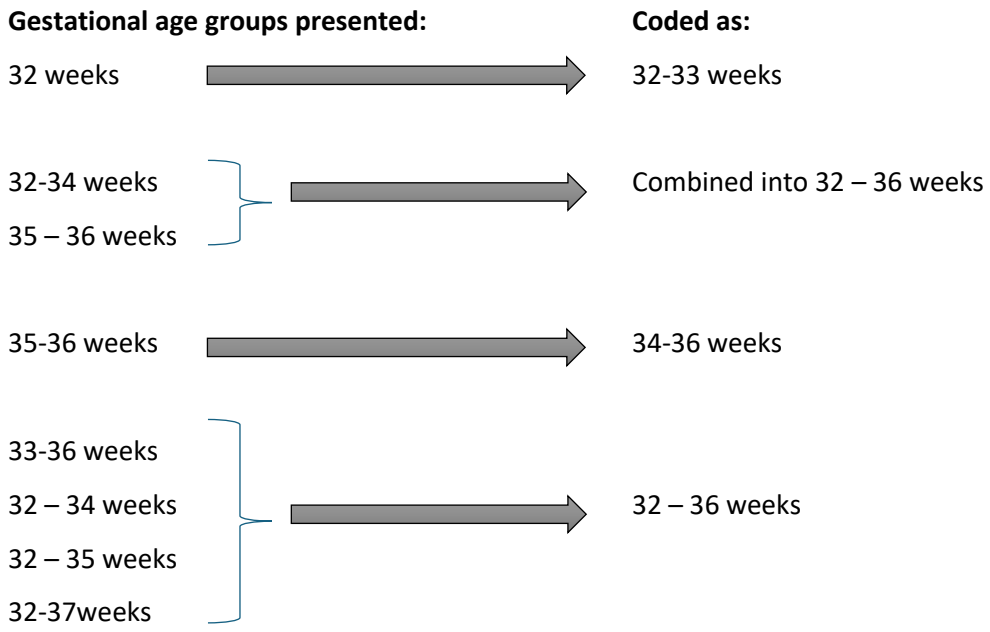
Each developmental disorder was considered individually. Children could not be included in the same meta-analysis twice, so where there were multiple papers using the same data, the most recent paper was used, unless an older paper presented data in a format that was easier to extract. Meta-analyses were conducted first to generate the unadjusted pooled relative risk of each developmental disorder by gestational age. Next, a separate meta-analysis was carried out to calculate the pooled prevalence of each developmental disorder by gestational age. This was undertaken using inverse-variance in Stata v. 17 (StataCorp., College Station, TX, USA) using the *metan* command for binary outcomes, the *meta* command for continuous outcomes, and the *metaprop* command for prevalence. Where results were presented as a continuous measure on a scale and a binary outcome was not also presented, the results across studies were combined using the Hedge's G standardised mean difference. If lower scores were not consistently indicative of greater impairment in the scales used across studies, then the signs were changed in order that the measures were comparable (Gøtzsche, Hróbjartsson, Marić et al., 2007). Random effects meta-analyses were used due to substantial heterogeneity anticipated between the studies. When there were zero cases a continuity correction of 0.5 was applied. The I squared statistic was used to assess heterogeneity.

For the calculation of prevalence, the Freeman Tukey arcsine transformation (*ftt*) was carried out where necessary, since it was anticipated that most of these disorders would have a low prevalence in the population; this transformation stabilises the variances before studies are pooled (Nyaga, Arbyn and Aerts, 2014; Barendregt, Doi, Lee et al., 2013). Publication bias was assessed using funnel plots created using the *meta* command in Stata.

Subgroup analyses by gestational age group were carried out where possible. The preferred groupings were as follows:

- moderately preterm (32-33 weeks)
- late preterm (34-36 weeks)
- early term (37- 38 weeks)

Where the results were not presented like this, in general a broader category was used as shown:



The 32-36 week category was only presented when there was no separate data available for children born at 32-33 weeks and 34- 36 weeks; it was decided that if a 32-33 week group and a 34-36 week group could be presented, a 32-36 week group would make relationships more complex to interpret, potentially without adding useful information.

2.2.6. Sensitivity analysis

The term comparator groups were variable across studies, for example ≥ 37 weeks gestation, >37 weeks, ≥39 weeks, 39-41 weeks, or 40 weeks. Therefore, a sensitivity analysis was undertaken for the relative risk of CP, global developmental delay and educational outcomes aged 6 -11 years including only studies which used a 'full' term comparison group (39-40/41 weeks gestation).

2.3. Results

2.3.1. Study selection

The initial search identified 10,473 non-duplicate studies for screening, see Figure 4. Fifteen further studies were added from reference screening. Seven additional studies were added following the repeat searches. 9,028 were excluded on title and abstract screening, which resulted in 1,467 studies for full text screening. At full text screening 1,371 papers were excluded, resulting in a total of 96 papers to include. Eighteen studies met the inclusion criteria but were not meta-analysed because the source cohort data had already been included via another publication, these papers are summarised in appendix 2.4.

The most common reasons for exclusion at the full text screening stage were:

- Wrong patient population e.g., born <32 weeks gestation, born pre 1996 (n = 465)
- Wrong article types i.e., conference presentations, commentaries, editorials, theses, dissertations/book chapters (n = 402)
- Wrong exposure, e.g., very low birth weight (n = 176)

There were several studies where the exposed children were 'very low birth weight'(VLBW), which means they were likely to be (but not definitely) preterm. These studies were excluded in order to facilitate clarity over the gestational ages of the exposed groups; the terms VLBW and prematurity should not be used synonymously (Emory, Savoie and Toomey, 1990).

There was substantial agreement with the second reviewer (CC) at both screening stages; 93.6% agreement with a Cohen's Kappa of 0.62 at abstract screening; 98.4% agreement with a Cohen's Kappa of 0.85 at full text screening (Watson and Petrie, 2010). There was full agreement between KP and CC when carrying out data extraction.

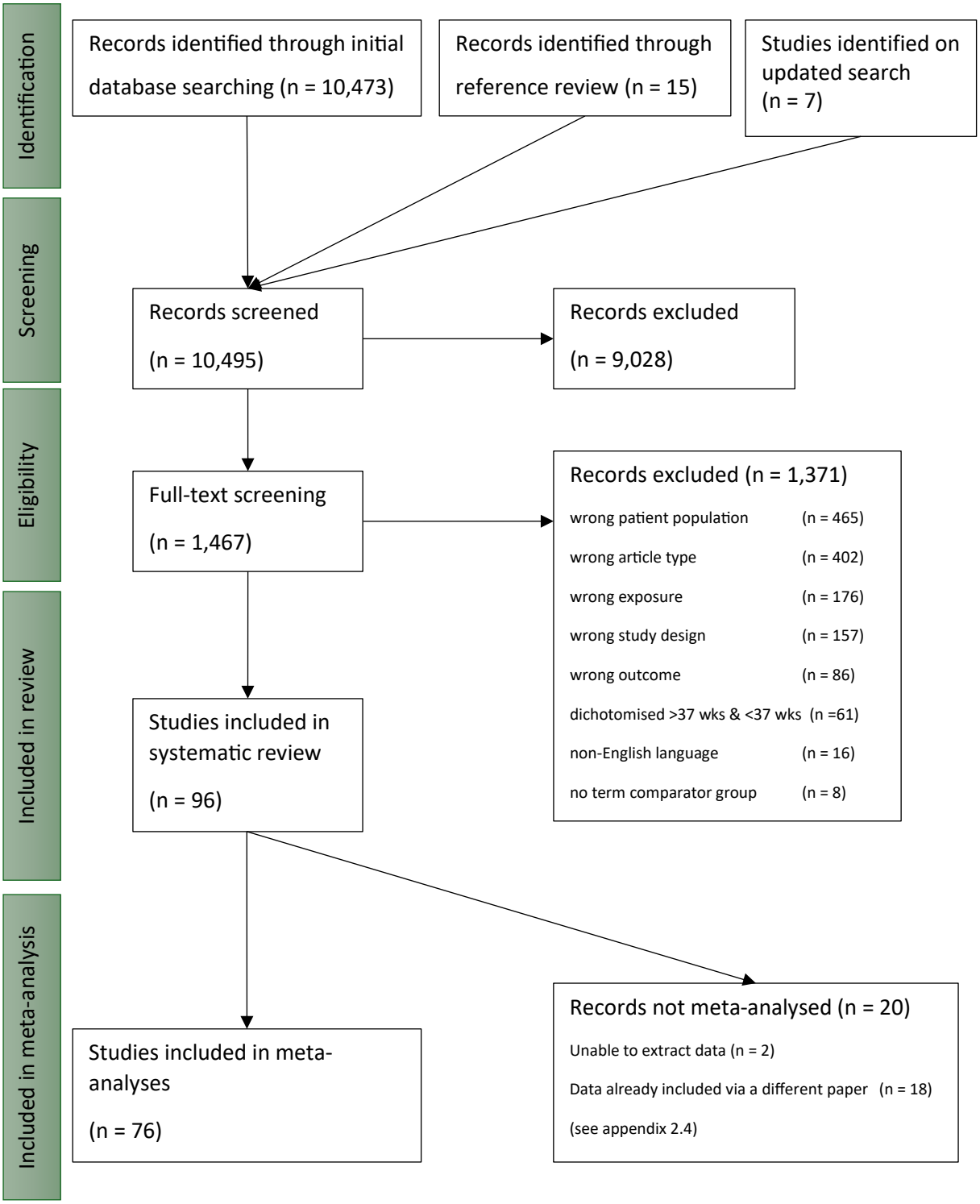


Figure 4 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Note not all the studies included in the systematic review were included in the meta-analysis

2.3.2. Study characteristics

The numbers of children and number of studies included in each meta-analysis are summarised in Table 4. Sample sizes ranged from 96 children to 1,390,601 children. The age at which participants were assessed ranged from 2 – 17 years. The majority of the included studies originated from more economically developed countries; 23/96 (24%) were from the USA, 13/96 (14%) from the UK and 11/96 (11%) from Australia. Several studies reported multiple outcomes. Feeding problems were not reported by any study.

Table 4 - Summary describing the number of studies used to calculate relative risk and number of participants per gestational age subgroup per outcome.

*Binary outcomes unless specified. Dark grey = no data; Blue = not presented (data available for both 32-33 week and 34-36 week groups). ADHD: attention deficit hyperactivity disorder. ASD: autism spectrum disorder. DCD: developmental co-ordination disorder. SEB: social, emotional, and behavioural problems. * this does not include Zambrana 2021, as only the results of the regression were presented therefore the raw numbers could not be extracted.*

Developmental disorder	32-33 weeks	32-36 weeks	34-36 weeks	37-38 weeks	Term	Total
Cerebral palsy						
number of children	15,365		87,053	346,859	2,695,512	3,144,789
number of studies	3		6	1	8	8
DCD						
number of children	2,445		13,636	42,394	88,244	146,719
number of studies	2		2	2	2	2
Visual impairment						
number of children	484	19,596		70,026	183,047	273,153
number of studies	1	4		1	5	5
Hearing impairment						
number of children	503	19,445		70,053	181,688	271,689
number of studies	1	2		1	3	3
Sleep apnoea						
number of children		22,039			377,952	399,991
number of studies		1			1	1
SEB global						
number of children	248		1,232	2,864	10,571	14,915
number of studies	2		2	1	2	2
SEB global (continuous)						
number of children		377	126		313	816
number of studies		1	1		2	2
SEB internalising						
number of children		597	53		4,368	5,018
number of studies		2	1		3	3
SEB externalising						
number of children		176			151	327
number of studies		1			1	1
SEB social						
number of children	84		594		813	1,491

Developmental disorder	32-33 weeks	32-36 weeks	34-36 weeks	37-38 weeks	Term	Total
number of studies	1		2		2	2
ADHD						
number of children		71,091	2,733	5,103	1,443,744	1,522,671
number of studies		3	2	1	5	5
ADHD (continuous)						
number of children		525	1,907	7,132	15,494	25,058
number of studies		3	3	2	7	7
ASD						
number of children	2,455		25,592	51,307	324,345	403,699
number of studies	2		3	1	3	3
Global dev. delay						
number of children	3,973		30,266	79,228	358,670	472,137
number of studies	1		3	1	3	3
Language delay						
number of children		745	1,673*	7,109*	31,272*	40,799*
number of studies		4	2	2	6	6
Motor delay						
number of children		522	1,414		7,108	9,044
number of studies		4	3		7	7
Cognitive delay						
number of children		525	1200		6,780	8,505
number of studies		4	1		5	5
Cognitive impairment						
number of children	631		1,315	135,185	540,350	677,481
number of studies	3		4	2	6	6
Cognitive impairment (continuous)						
number of children	31		564	469	11,529	12,593
number of studies	1		4	1	5	5
Executive function (continuous)						
number of children		45	39		90	174
number of studies		1	1		2	2
School readiness						
number of children	199		14,485	29,238	239,737	283,659
number of studies	2		6	4	7	7
Low educational attainment 6-11 years						
number of children	2,215		40,586	60,995	472,354	576,150
number of studies	2		5	4	6	6
Low educational attainment 12-17 years						
number of children	76		401	28,948	83,073	112,498
number of studies	1		1	2	2	2
SEND						
number of children	8,429		53,178	129,778	1,053,459	1,244,844
number of studies	3		5	3	6	6

2.3.3. Risk of bias assessment

16 studies were 'fair' quality; 78 were 'good' quality (Table 5). Two studies (Oros 2014 and Zhou 2020) were cross sectional and therefore the last two questions of the Newcastle Ottawa Scale do not apply, and so they were not classified as good/fair/poor quality. No studies were classified as poor quality. The lowest scoring section was 'Outcome', largely driven by low scores for question 7 – "assessment of outcome". In order to score for this question, the assessment needs to be either an independent blind assessment or ascertained by data linkage. However, in many cases (50% of studies) outcome was determined either via completion of a (validated) questionnaire by parents or was not clear. The highest scoring section was 'Selection', this was largely because many of the studies used longitudinal birth cohort studies, where the outcome of interest could not be present at the start of the study (question 4) and the non-exposed cohort was part of the same community as the exposed cohort (question 2).

Table 5 - Risk of bias assessment

Orange = 'fair quality', green = 'good quality'

Record ID	Selection				Comparability		Outcome			total
Al-Haddad 2017	0	0	0	1	0	0	0	1	1	3
Alterman 2021	1	1	1	1	1	1	0	1	0	7
Alterman 2022	1	1	1	1	1	1	0	1	0	7
Arnaud 2007	1	1	1	1	1	1	0	1	1	8
Ask 2018	1	1	1	1	1	1	0	1	0	7
Bailhache 2022	1	1	0	1	1	1	0	1	0	6
Baron 2009	0	1	0	1	0	0	1	1	1	5
Baron 2011	1	0	0	1	1	1	1	1	1	7
Baron 2012	0	0	0	1	0	0	1	1	1	4
Baron 2014	0	1	0	1	1	1	1	1	1	7
Beauregard 2018a	1	1	1	1	1	1	1	1	1	9
Beauregard 2018b	1	1	1	1	1	1	1	1	1	9
Beer 2022	1	1	1	1	1	1	1	0	1	8
Bentley 2016	1	1	1	1	1	1	1	1	1	9
Berry 2018	1	1	1	1	0	0	1	1	1	7
Brown 2019	0	1	0	1	1	1	1	1	0	6
Brumbaugh 2014	0	1	1	1	0	0	0	1	1	5
Bul 2012	1	1	0	1	0	1	0	1	1	6
Chan 2014	1	1	1	1	1	1	1	1	0	8
Chen 2014	1	1	1	1	1	1	0	1	1	8
Chen 2020	1	1	1	1	1	1	1	1	1	9
Chen 2022	1	1	1	1	1	1	1	1	1	9
Cheong 2017	1	1	1	1	0	1	1	1	1	8
Crockett 2022	1	1	1	1	1	1	1	1	1	9

Record ID	Selection				Comparability		Outcome			total
Cronin 2016	1	1	1	1	1	1	0	1	1	8
Cserjesi 2012	1	1	1	1	1	1	1	1	1	9
Curry 2012	1	1	1	1	0	0	1	1	1	7
Darlow 2009	1	1	0	1	0	0	1	1	1	6
De Jong 2015	0	1	0	1	0	1	0	1	1	5
Demestre 2015	1	1	1	1	1	1	1	1	1	9
Dhamrait 2021	1	1	1	1	1	1	1	1	1	9
Drougia 2007	1	1	1	1	1	1	1	0	1	8
Faleschini 2020	1	1	1	1	1	1	0	1	1	8
Fitzpatrick 2016	1	1	1	1	1	1	0	1	0	7
Guy 2015	1	1	1	1	0	1	0	0	0	5
Hanly 2018	1	1	1	1	1	1	1	1	1	9
HigaDiez 2015	1	1	1	1	1	1	0	1	1	8
Hirvonen 2014	1	1	1	1	1	1	1	1	1	9
Hodel 2016	0	1	1	1	0	0	0	1	1	5
Hornman 2016	1	1	1	1	1	1	0	1	1	8
Hornman 2017	1	1	1	1	1	1	0	1	1	8
Hua 2021	1	1	1	1	1	1	0	1	0	7
Johnson 2015a	1	1	1	1	1	1	0	1	0	7
Johnson 2015b	1	1	1	1	1	1	0	0	0	6
Kern 2007	0	0	0	1	1	0	0	1	1	4
Kerstjens 2011	1	1	1	1	1	1	0	1	1	8
Kerstjens 2012	1	1	1	1	1	1	0	1	1	8
Klassen 2004	1	0	0	1	0	0	0	1	0	3
Kuzniewicz 2014	1	1	1	1	1	1	1	0	1	8
Larroque 2008	1	1	1	1	1	1	0	1	0	7
Larsen 2021	1	1	1	1	0	0	1	0	1	6
Leavey 2013	1	1	1	1	1	1	1	0	1	8
Libuy 2023	1	1	1	1	1	1	1	1	0	8
Lingasubramanian 2022	1	1	1	1	1	1	1	1	0	8
Marotta 2020	0	0	0	1	1	1	0	1	1	5
Morse 2009	1	1	1	1	1	1	1	0	1	8
Nepomnyaschy 2012	1	1	1	1	1	1	1	1	0	8
Oros 2014	0	1	0	1	0	0	1	cross sectional		3/7
Patil 2014	0	1	1	1	0	0	0	1	1	5
Pérez-Pereira 2014	0	0	0	1	0	0	0	1	1	3
Pérez-Pereira 2020	0	0	1	1	1	1	0	1	1	6
Petrini 2009	1	1	1	1	1	0	1	1	1	8
Pettinger 2020	1	1	1	1	1	1	1	1	1	9
Polic 2017	0	0	1	1	1	1	0	1	1	6
Potijk 2012	1	1	1	1	1	1	0	1	1	8

Record ID	Selection				Comparability		Outcome			total
Potijk 2013	1	1	1	1	1	1	0	1	1	8
Potijk 2015	1	1	1	1	1	1	0	1	1	8
Potijk 2016	1	1	1	1	1	1	0	1	1	8
Poulsen 2013	1	1	1	1	1	1	1	1	1	9
Quigley 2012	1	1	1	1	1	1	1	1	0	8
Raynes-Greenow 2012	1	1	0	1	1	0	1	1	1	7
Reuner 2015	1	0	0	1	1	1	0	1	0	5
Richards 2015	1	1	1	1	1	1	1	1	1	9
Richards 2016	1	1	1	1	1	1	1	1	1	9
Robaei 2006	1	1	0	1	0	0	0	1	1	5
Schneider 2014	0	0	0	1	1	1	1	1	1	6
Searle 2017	1	1	1	1	1	1	1	1	1	9
Shah 2016a	1	1	1	1	1	1	1	1	0	8
Shah 2016b	1	1	1	1	1	1	0	1	1	8
Smithers 2015	1	1	1	1	1	1	1	1	1	9
Stene-Larsen 2014	1	1	1	1	1	1	1	1	0	8
Strand 2013	1	1	1	1	1	1	1	1	1	9
Talge 2012	1	1	1	1	1	1	0	0	0	6
Tso 2022	1	1	1	1	1	1	1	1	1	9
Van Baar 2009	1	1	0	1	0	1	0	1	1	6
Voight 2012	1	0	0	1	0	1	0	1	1	5
Wehby 2022	1	1	1	1	1	1	1	1	0	8
Williams 2013	1	1	1	1	1	1	1	1	1	9
Woythaler 2011	1	1	1	1	1	1	0	1	1	8
Woythaler 2015	1	1	1	1	1	1	1	1	0	8
Yang 2010	0	1	1	1	1	1	0	1	1	7
You 2019a	1	1	0	1	1	1	1	1	1	8
You 2019b	0	0	0	1	0	0	0	1	1	3
Zambrana 2021	1	1	1	1	1	1	1	1	0	8
Zhou 2020	1	1	1	1	1	1	0	cross sectional		6/7
Zhu 2012	1	1	1	1	1	0	0	1	1	7

2.3.4. Meta analyses

Cerebral Palsy (CP)

CP was reported by twelve studies (Table 6). There was a total of 3,144,789 children from eight studies included in the meta-analysis. Arnaud (2007) reported CP as an outcome, but these children were already included in the meta-analysis via Larroque (2008); both studies used data from the French birth cohort study EPIPAGE (Etude Epidemiologique sur les Petits Ages Gestationnels). Cheong (2017), Darlow (2009) and Strand (2013) all presented only 32-36 week groups, which as per the methods were not included in the meta-analysis, as results from 32-33 weeks and 34-36 weeks were available.

Three of the included studies (Larroque 2008, You 2019a, You 2019b) carried out formal examinations of the participants as opposed to using linked records. This may explain why these studies all had higher prevalence of CP.

As shown in Figure 5 and Figure 6 the relative risk and the prevalence of CP increases as gestational age decreases. This can be seen even at 37-38 weeks, although only one study (Chen 2022) reported this gestational age group.

Table 6 – Studies reporting cerebral palsy by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% diff. between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria used	Study Quality
(Chen, Sjolander, Johansson et al., 2022)	Sweden	(32-36 weeks: 77,986) 37-38 weeks: 346,859 39-40 weeks: 965,756	0-16 years (median 9.4 years)	1998–2016	50.4% (not reported by gestation)	Not reported (NR)	Diagnostic codes in linked records	good
(Drougia, Giapros, Krallis et al., 2007)	Greece	34-36 weeks: 594 ≥37 weeks: 1,719	Minimum 2 years	1997–2003	NR	NR	Diagnosis in medical records	good
(Hirvonen, Ojala, Korhonen et al., 2015)	Finland	32-33 weeks: 4,862 34-36 weeks: 28,152 ≥37 weeks: 671,988	7 years	1996–2008	32-33 weeks: 54.9% 34-36 weeks: 54.2% ≥37 weeks: 50.8%	NR	Diagnostic codes in linked records	good
(Larroque, Ancel, Marret et al., 2008)	France	32 weeks: 510 39-40 weeks: 395	5 years	1997	52% male	NR	Neurological examination	good
(Larsen, Wiingreen, Jensen et al., 2021)	Denmark	32-33 weeks: 9,993 34-36 weeks: 49,752 37-41 weeks: 926,367	4-6 years	1997–2013	NR - only reported for each disorder not each gestation	NR	Linked CP registries	good
(Petrini, Dias, McCormick et al., 2009)	USA	34-36 weeks: 8341 37-41 weeks: 128,955	1 - 5 years	2000 - 2004	34-36 weeks: 54.4% 37-41 weeks: 50.9%	Hispanic: 24.5%; Asian: 18.2%; White: 41.5%; Unknown: 8.5%; Black:7.3%	Diagnostic codes in linked records	good
(You, Shamsi, Hao et al., 2019a)	China	34-36 weeks: 102 37–42 weeks: 153	24-30 months	2011 - 2013	34-36 weeks: 66.7% 37–42 weeks: 61.4%	NR	Neurological examination	good
(You, Yang, Hao et al., 2019b)	China	34-36 weeks: 112 37–42 weeks: 179	2 years	2013 -2015	34-36 weeks: 54.5%, 37–42 weeks: 47.5%	NR	Neurological examination	fair

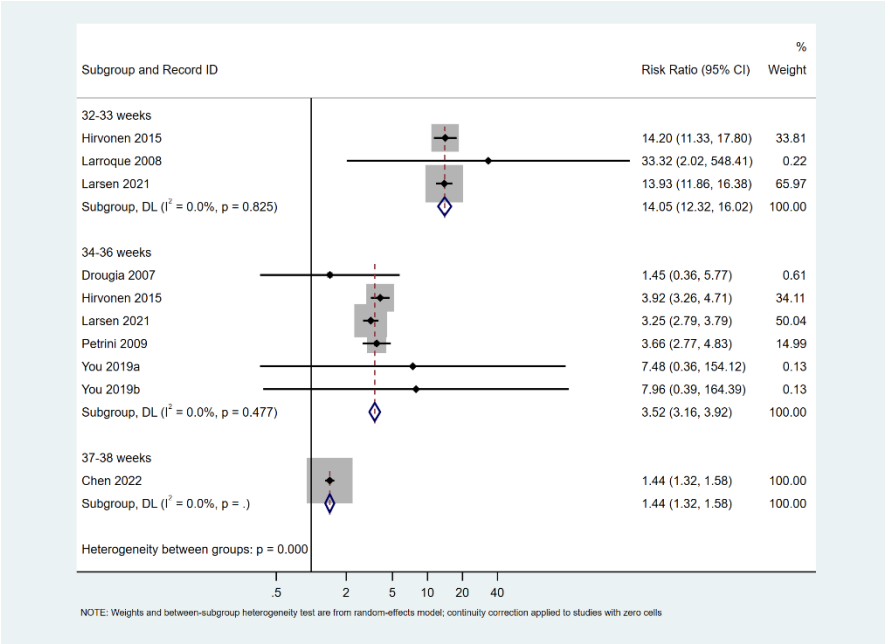


Figure 5 - Relative risk of cerebral palsy by gestational age.

95% CI = 95% confidence intervals.

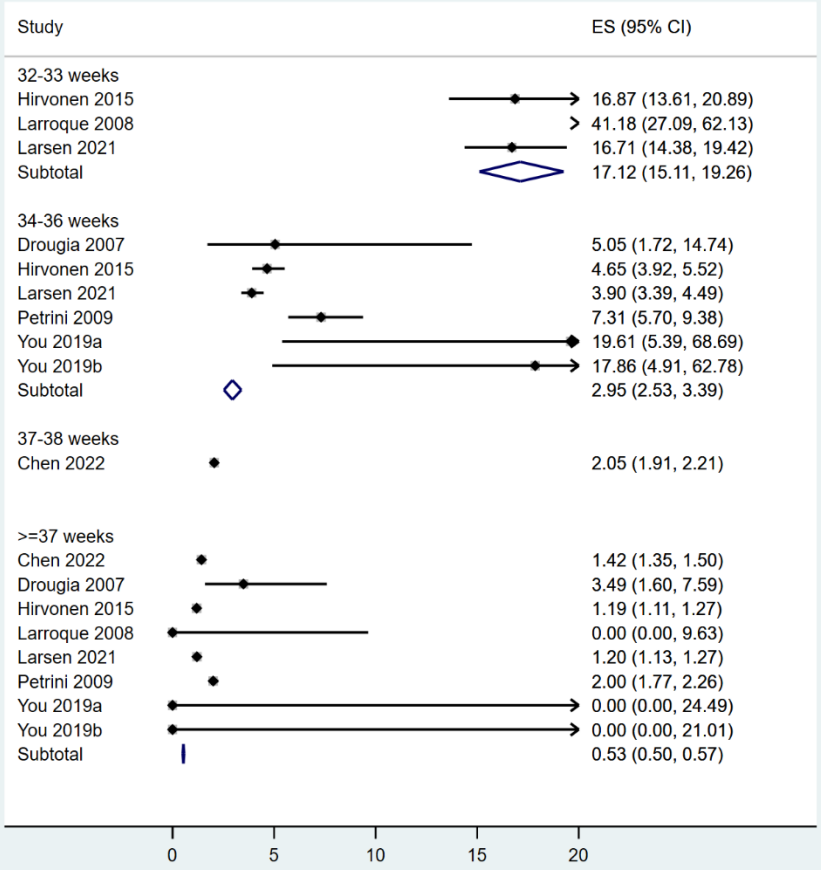


Figure 6 - Prevalence of cerebral palsy by gestational age, per 1,000 children.

ES = Estimate Size. 95% CI = 95% confidence intervals.

Motor function problems

There were three studies reporting (non-CP) motor function problems (Table 7). Two (Hua 2021, Zhu 2012) were investigating developmental co-ordination disorder (DCD), whereas Arnaud (2007) was investigating "minor neuromotor dysfunctions". Arnaud (2007) used data from the French birth cohort study EPIPAGE. These children had a Touwen examination aged 5 years. The authors found that there was an inverse dose response relationship with gestational age for 'mild' minor neuromotor dysfunction (affecting one or two subsystems); 138/356 children at 32 weeks, 60/195 children at 33-34 weeks, and 63/287 children at 39-40 weeks. This relationship is less clear for 'moderate' minor neuromotor dysfunctions, but that may be because of low numbers of diagnoses: only 10 diagnoses amongst children born at 32-40 weeks gestation.

Combining these three studies would be possible but not meaningful and so a meta-analysis of DCD was carried out. There was a total of 146,719 children included across two studies. The studies were from different settings; one was European and used the Developmental Coordination Disorder Questionnaire (Zhu, Olsen and Olesen, 2012) and one was from China and used Little Developmental Coordination Disorder Questionnaire (Hua, Barnett, Williams et al., 2021).

There seems to be an inverse relationship between risk of DCD and gestational age (Figure 7). However, for the 32-33 week group this did not reach statistical significance, with the confidence intervals crossing one. The prevalence of DCD was markedly different between the studies (Figure 8). This could be related to the different assessment tools used or the age at which the assessments were carried out. Zhu (2012) assessed the children aged 7, in Hua (2021) they were 3 -5 years old. It is possible that there are some younger children who screen positive for DCD at a younger age, but their motor skills improve as they grow.

Table 7 - Studies reporting motor function problems by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (of whole cohort unless > 1% diff. between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria used	Study Quality
(Arnaud, Daubisse-Marliac, White-Koning et al., 2007)	France		5 years	1997	33-34 weeks: 50.7% 39-40 weeks: 51.2%	Not reported (NR)	Touwen examination	good
(Hua et al., 2021)	China	32-33 weeks: 2,322 34-36 weeks: 12,915 37-38 weeks: 38,875 39-40 weeks: 76,501	3 - 5 years	2013-2016	32-33 weeks: 54.0% 34-36 weeks: 55.3% 37-38 weeks: 55.3% 39-40 weeks: 51.6%	Han Chinese 99%	Little Developmental Coordination Disorder Questionnaire	good
(Zhu et al., 2012)	Denmark	32-33 weeks: 123 34-36 weeks: 721 37-38 weeks: 3,519 39-40 weeks: 11,743	7 years	1996-2002	51%	NR	Developmental Coordination Disorder Questionnaire	good

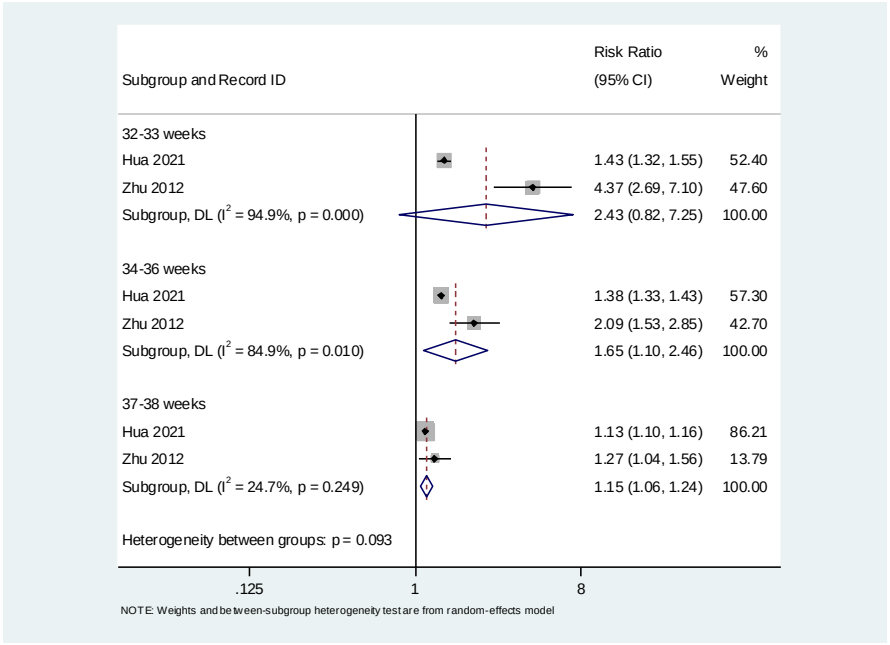


Figure 7 - Relative risk of Developmental co-ordination disorder (DCD) by gestational age

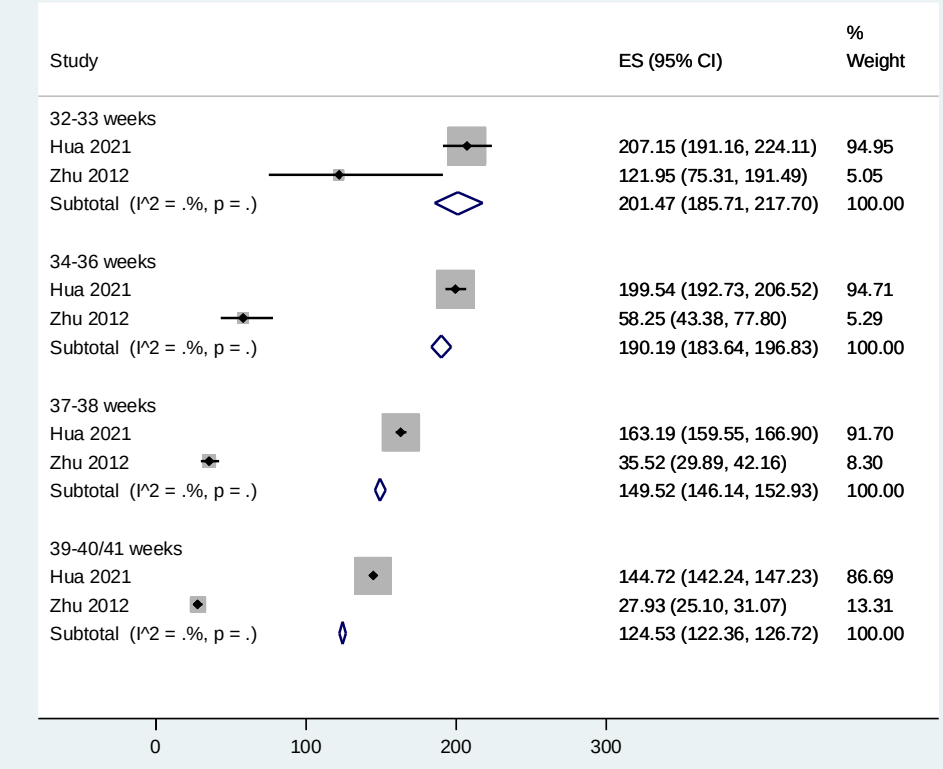


Figure 8 – Prevalence of Developmental co-ordination disorder (DCD) by gestational age, per 1,000 children

Visual Impairment

There was a total of 273,153 children included in this meta-analysis across five studies. As shown below (Table 8) the studies used one of two markedly different approaches to detect visual impairment: 3/5 studies carried out optometry and ophthalmic examinations, whereas 2/5 asked parents whether the child had visual impairment as part of a standardised survey. Klassen (2004) is an unusual study as it only considers children who were admitted to a neonatal unit, so the term children in the comparator group are not typical. Larroque (2008) is the only study that specifically investigated children born at 32-33 weeks.

There is an increase in the relative risk of visual impairment when born at 32-38 weeks (Figure 9), which reaches statistical significance in the 37-38 week group (although outcomes for the early term group are only reported by one study). Visual impairment is more prevalent amongst children born at 32-38 weeks compared to children born at term (Figure 10).

Table 8 - Studies reporting visual impairment as an outcome by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% between gestational age groups)	Ethnicity of participants using same terminology as the studies (of whole cohort or of term group)	Tool / criteria used	Study Quality
(Al-Haddad, Fattah, Smeets et al., 2017)	Lebanon	32-36 weeks:51 ≥ 37 weeks: 69	4.9 years (mean)	2006 - 2014	55%	Not reported (NR)	Visual impairment on examination	fair
(Berry, Foster, Rowe et al., 2018)	New Zealand	33-36 wks: 19,089 37-38 wks: 70,026 39 -40 wks: 180,987	6 - 11 years	1998 - 2000 and 2005 - 2015	51.4%	European 67%, Pacific Islander 12% Māori 21%	Parental report 'Under care for vision'	good
(Klassen, Lee, Raina et al., 2004)	Canada	33-37 weeks: 341 >37 weeks: 259	3.5 years	1996-1997	33-37 weeks: 45.2% >37 weeks: 40.2%	NR	Reported Problem reported on the Health Status Classification System-Preschool (HSCS-PS) questionnaire.	fair
(Larroque et al., 2008)	France	32 weeks: 484 39-40 weeks: 389	5 years	1997	52% male	NR	Visual deficiency: Less than 3/10 for one or both eyes, assessed, without correction, with the Rossano test	good
(Robaei, Kifley, Gole et al., 2006)	Australia	32-36 weeks: 115 ≥37 weeks: 1,343	6 years	1997-1998	32-36 weeks: 52% ≥37 weeks: 51%	White 65.9% Southeast Asian 15.5% Other 18.5%	Visual acuity in the lowest quartile (worse eye) uncorrected	fair

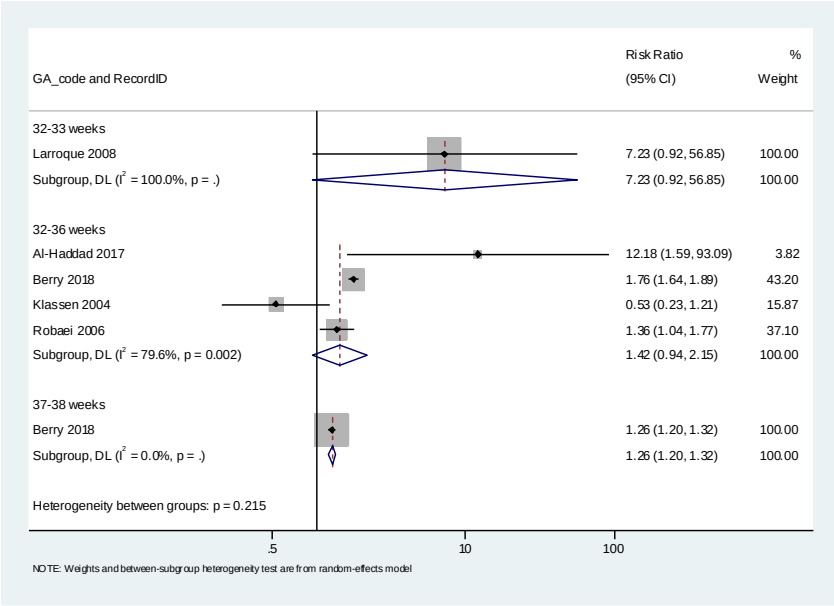


Figure 9 – Relative risk of visual impairment by gestational age

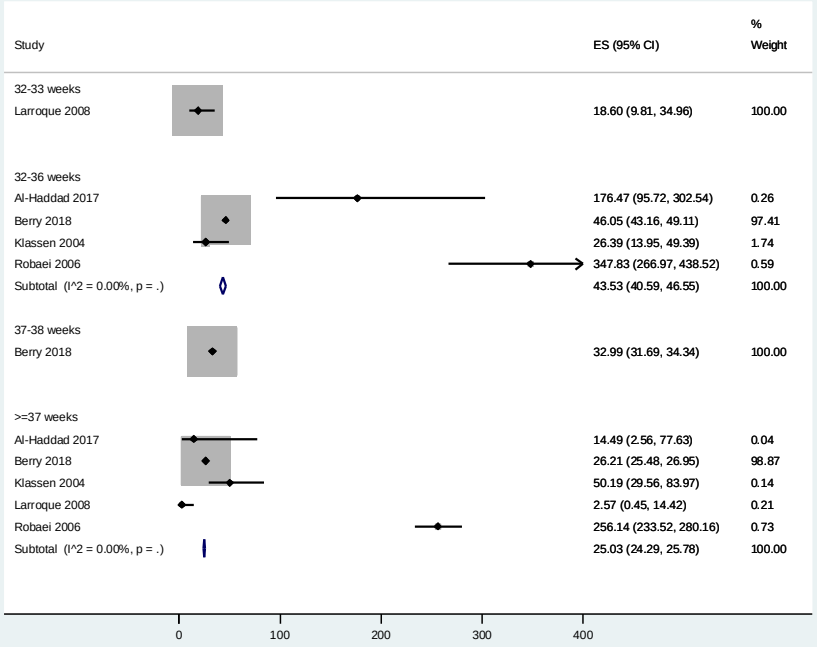


Figure 10 - Prevalence of visual impairment by gestational age, per 1,000 children

Hearing Impairment

There was a total of 271,689 children included in this meta-analysis from three studies (Table 9). All these studies relied on parental report of difficulties.

The relative risks of hearing impairment are not significant for any gestational age group born before full term (Figure 11). However, similarly to visual impairment, in the 32-36 week group there is an increased prevalence of hearing impairment compared to the term group (Figure 12). This effect is not seen in the 32-33 week group, but that was only one relatively small study (Larroque et al., 2008).

Klassen (2004) is an unusual study as it only considers children who were admitted to the neonatal intensive care unit, so the term children are not 'typical'. The results of this meta-analysis are largely driven by Berry (2018) which is a much larger study than the other two.

Table 9 - Studies reporting hearing impairment by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% diff. between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria used	Study Quality
(Berry et al., 2018)	New Zealand	33-36 weeks: 19,104 37-38 weeks: 70,053 39 -40 weeks: 181,041	6 - 11 years	1998 - 2000 and 2005 - 2015	51.4%	European 67%, Pacific Islander 12% Māori 21%	Under care for hearing	good
(Klassen et al., 2004)	Canada	33-37 weeks: 341 >37 weeks: 259	3.5 years	1996-1997	33-37 weeks: 45.2% >37 weeks: 40.2%	Not reported (NR)	Reported Problem on HSCS-PS Health Attribute	fair
(Larroque et al., 2008)	France	32 weeks: 503 39-40 weeks: 388	5 years	1997	52% male	NR	Hearing deficiency for one of both ears on medial questionnaire	good

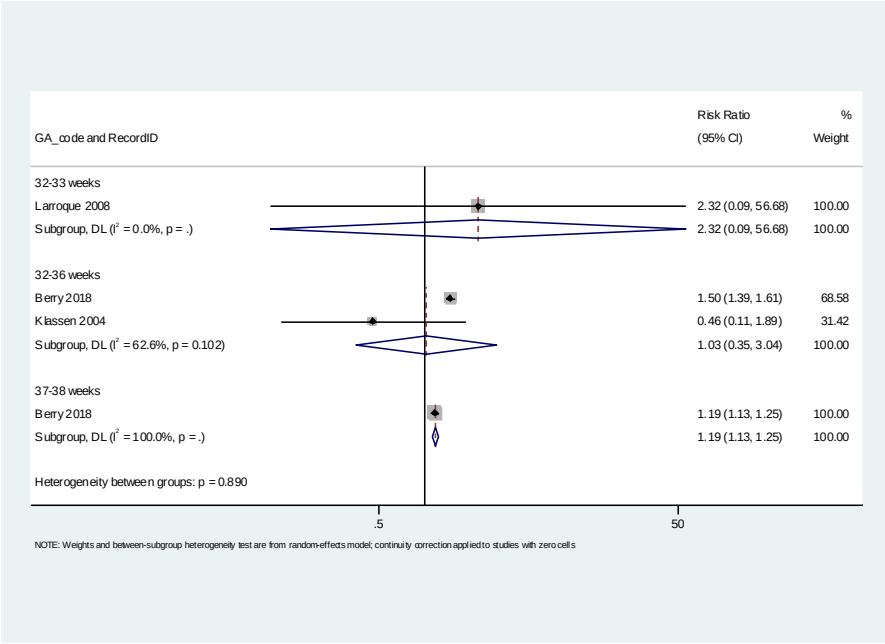


Figure 11 - Relative risk of hearing impairment, by gestational age

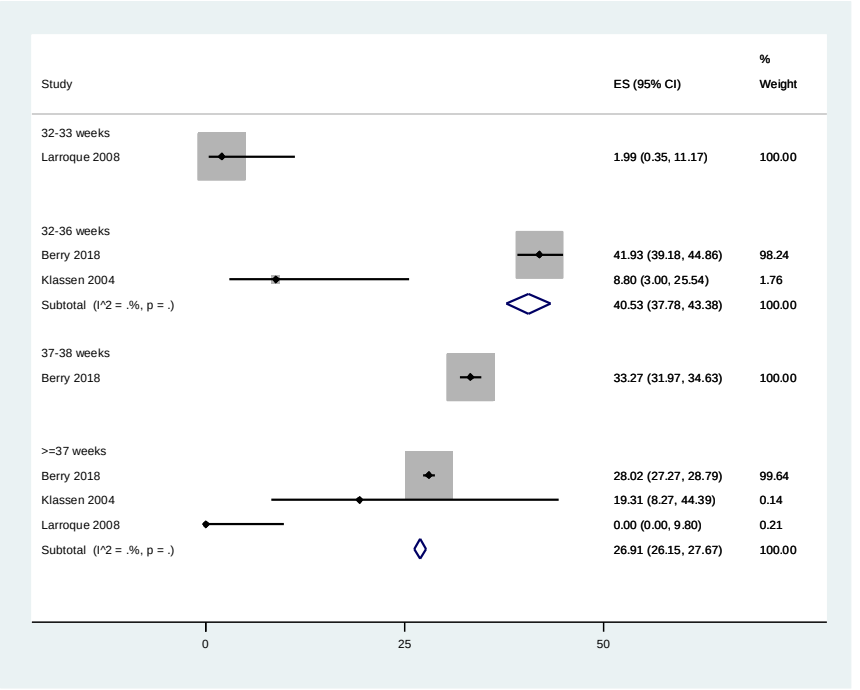


Figure 12 – Prevalence of hearing impairment by gestational age, per 1,000 children

Sleep Apnoea

There was only one study which reported sleep apnoea as an outcome; 399,991 children were included (Table 10). The relative risk and prevalence of sleep apnoea is increased amongst children born at 32-36 weeks compared to children born at term, but this is based on only one study (see Figure 13 and Figure 14).

Table 10 – Study reporting sleep apnoea as an outcome by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria used	Study Quality
Raynes-Greenow 2012	Australia	32-36 weeks: 22,039 ≥37 weeks: 377,952	2-6 years	2000 - 2004	51.4%	Not reported (NR)	Diagnosis of sleep apnoea in medical notes	good

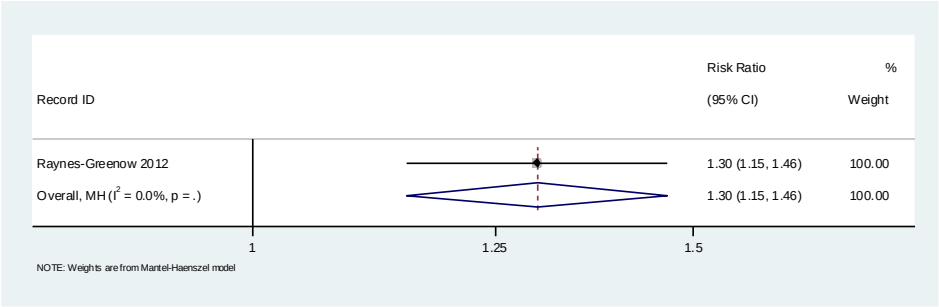


Figure 13 - Relative risk of sleep apnoea by gestational age

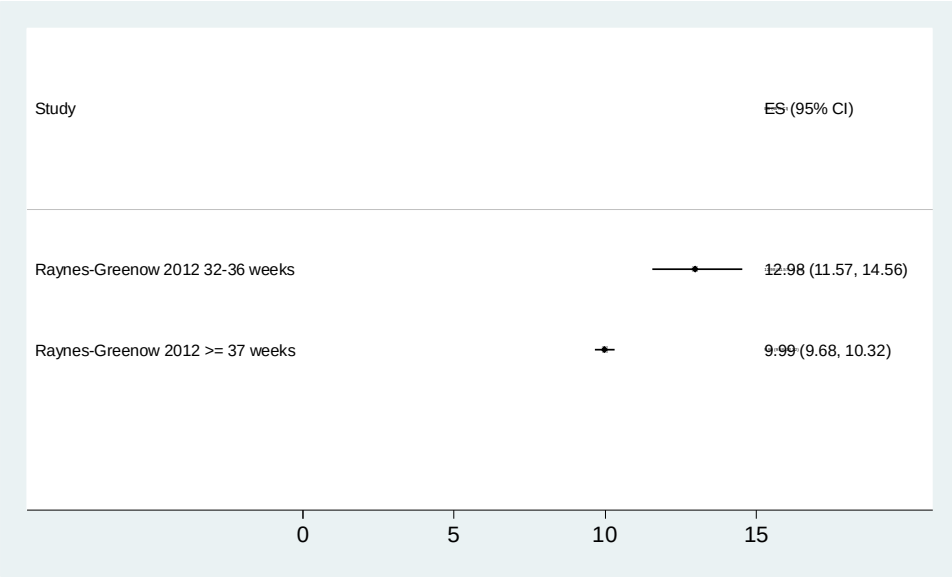


Figure 14 - Prevalence of sleep apnoea by gestational age, per 1,000 children

Social, Emotional, and Behavioural Problems

The papers which report social, emotional, and behavioural outcomes are described in Table 11. The various tools to screen for or diagnose social, emotional, and behavioural problems are summarised in Table 12. Some of the tools have a hyperactivity subscale e.g., the ADHD subscale on the Child Behaviour Checklist (CBCL) and these were analysed with the studies reporting ADHD.

"Total difficulties" or global scores were extracted preferentially, but if these were not presented, the internalising and externalising scores were extracted, broken down to match other studies as closely as possible. Internalising behaviours are those which are 'inside' oneself, such as anxiety or depression, whereas externalising behaviours are 'outside' oneself, for example 'delinquency' and aggression (Polic, Bubic, Mestrovic et al., 2017). If a study was included in the 'global' problems meta-analysis, it was not also included in the internalising or externalising behaviours meta-analyses.

Three studies presented social problems as a distinct outcome. These were analysed separately as they could not meaningfully be combined with the other meta-analyses. You (2019b) reports 'social competence', but the tool used was a measure of practical, self-care skills, as opposed to competence in understanding social interaction as in the other studies, so was not included here. Cheong (2017) presented social-emotional competence subscales of the ITSEA, but this was not meta-analysed, as the authors only presented 32-36 week group and in this meta-analysis, we were able to present data for 32-33 weeks and 34-36 weeks separately.

The following studies were excluded from the meta-analyses: Potijk (2012), Potijk (2016) and Hornman (2016) all used data from the Longitudinal Preterm Outcome Project (LoliPOP), which had already been included via Potijk (2015), where the data was presented in a format which was easier to extract. However, Potijk (2015) only presented 32-36 week group and so this was not presented in the meta-analysis. None of the other papers using this cohort of children presented data in a way that would have been able to be meta-analysed based on the pre-specified method. Like several other studies investigating social, emotional, and behavioural outcomes, Berry 2018 used the strengths and difficulties questionnaire (SDQ). The authors present mean scores for four subscales for 33-34 weeks, 35-36 weeks, 37-38 weeks, and 39-40 weeks. However, no standard deviations, standard errors, or confidence intervals were provided. The authors were contacted but did not respond. Chen (2014) also reported social, emotional, and behavioural outcomes using the SDQ, however, it was not possible to include it in the meta-analysis because only the

results of the regression were presented, and it was unclear exactly how many children were in each group. The authors were contacted but did not respond. This resulted in five meta-analyses, including the following number of children:

- Global behavioural problems (binary): 14,915
- Global problems (continuous): 816
- Internalising behaviours: 5,018
- Externalising behaviours: 327
- Social problems: 1,491

Table 11 - Studies reporting social, emotional, or behavioural problems by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% diff. between different gestational ages)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Subscale extracted for meta-analysis	Study Quality
(Bailhache, Monnier, Moulin et al., 2022)	France	32-36 weeks: 421 ≥37 weeks: 4164	9 years	2011	50.9%	Not reported (NR)	Strengths and Difficulties Questionnaire (SDQ)	Emotional symptoms	good
(Chen, Claessens and Msall, 2014)	Australia	Excluded from meta-analysis – unable to extract data	4.75 years (mean)	1999, 2000, 2004	51%	NR			good
(Cheong, Doyle, Burnett et al., 2017)	Australia	32-36 weeks: 176 ≥37 weeks: 151 (Internalising and externalising)	2 years	2009- 2012	32-36 weeks: 47.8% ≥37 weeks: 53.2 %	NR	Infant Toddler Social and Emotional Assessment (ITSEA)	Externalizing behavior; Internalizing behavior	good
(Cronin et al., 2016)	UK	32–33 weeks: 164 34–36 weeks: 691 37-38 weeks: 2,864 39-41 weeks: 9,811	5 years	2002	32-33 weeks: 57.3% 34-36 weeks 53.7% 37-38 weeks 51.9% 37-41 weeks 50.6%	White British 87.9%	Strengths and Difficulties Questionnaire (SDQ)	Total Difficulties	good
(de Jong, Verhoeven, Lasham et al., 2015)	Netherlands	Excluded from MA, only presented 32-36 week group	4 years	2010-2011	32-36 weeks 57.8% >37 weeks: 45.5%	Dutch 95.9%	Child Behaviour Checklist (CBCL)	Total Difficulties	fair
(Hornman, de Winter, Kerstjens et al., 2016)	Netherlands	Excluded – data would be included via Potijk (2015)	4 years	2002-2003	Preterm 54.6% Term 47.6%	Non-Dutch birth country 8.3%			good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% diff. between different gestational ages)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Subscale extracted for meta-analysis	Study Quality
(Johnson et al., 2015c)	UK	32–33 weeks: 84 34–36 weeks: 541 ≥37 weeks: 760	2 years	2009- 2010	32-36 weeks 53.8% Term 50.2%	White 78.6%; Asian or Asian British 4.7%; Black or Black British 3.6%; Mixed 2.0 %; Chinese or other 1.0 % Unknown 0.2 %	Brief Infant Toddler Social Emotional Assessment (BITSEA)	Behavior problems; social competence	good
(Klassen et al., 2004)	Canada	Excluded from MA, only presented 32-36 week group	3.5 years	1996-1997	33-37 weeks: 45.2% >37 weeks: 40.2%	Not reported (NR)			fair
(Marotta, Rea, Ferri et al., 2020)	Italy	34-36weeks: 53 ≥37weeks: 53	5 - 11 years (mean 8)	2002-2010	39.6%	NR	Intelligence and Development Scales (IDS)	Emotion Regulation. Social Behavioural Competence	fair
(Polic et al., 2017)	Croatia	34-36 weeks: 126 37-40 weeks: 131	6 - 12 years	2002-2008	34-36 weeks: 56.3% 37-40 weeks: 59.5%	NR	Child Behaviour Checklist (CBCL)	"Total" problems	good
(Potijk, De Winter, Bos et al., 2012)	Netherlands	Excluded – data would be included via Potijk 2015	3 years	2002-2003	32-35 weeks: 57.2% 38-41 weeks: 49.2%	NR			good
(Potijk, de Winter, Bos et al., 2015)	Netherlands	Excluded from MA, only presented 32-36 week group	3 years	2002-2003	54.2%	Dutch: 94.6%			good
(Potijk, de Winter, Bos et al., 2016)	Netherlands	Excluded – data would be included via Potijk 2015	4 years	2002-2003	NR	NR			good
(van Baar, Vermaas, Knots et al., 2009)	Netherlands	32-36 weeks: 377 ≥37 weeks: 182	8 years	1996 - 1999	Preterm 52% Term 47%	Dutch 91%	Child Behavior Check List (CBCL)	“Total” problems	good

Table 12 - Summary of tools used to screen for social, emotional, and behavioural problems

Tool	Details including Subscales	Used in the following studies	Scale / Subscales extracted	Meta analysis study is included in:
Child Behavior Check List (CBCL)	The CBCL is slightly different when translated and when used in different age groups, hence the subscales for each form are different. It consists of 100-120 questions measuring behavioural problems / symptoms which map onto the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), including ADHD symptoms (Bul and van Baar, 2012). Some authors presented all the subscales; some presented a total score (Polic et al., 2017; de Jong et al., 2015; Potijk et al., 2015; van Baar et al., 2009), some presented internalising (anxious, depressed, somatic complaints) and externalising (rule-breaking, aggressive behavior) broadband scales (Polic et al., 2017). Higher scores indicate greater need for intervention (Polic et al., 2017)	Bul 2012	ADHD subscale	ADHD – continuous
		deJong 2015	Total score	Global - binary
		HigaDiez 2016	Delinquent/aggressive behaviour	Externalising behaviour
			Attention problems	ADHD – binary
		Polic 2017	Total score	Global - continuous
		Potijk 2015	Total score	Global - binary
		Van Baar 2009	Total score	Global -continuous
Conners Parent Rating Scale–Revised (CPRS-R:S) and Conners Teacher Rating Scale–Revised Short Form (CTRS-RSF)	The CPRS-R:S has four outputs designed to reflect criteria from the DSM-IV (DSM-IV) (Achenbach, Dumenci and Rescorla, 2003).; Oppositionality (irritability, anger-proneness, defiance) Inattention (difficulty concentrating, planning, or maintaining attention) Hyperactivity (impulsivity, restlessness) ADHD index (inattention and hyperactivity) (Talge, Holzman, Van Egeren et al., 2012). Higher scores on the CPRS-R:S are associated with a diagnosis of ADHD. (Conners, 2001). Unlike the other studies, Lingasubramanian et al. used the Teacher's version of the questionnaire.	Ask 2018	n/A – only selected items reflecting ADHD were asked	ADHD – continuous
		Talge 2012	ADHD Index	ADHD – continuous
		Lingasubramanian 2022	ADHD index	ADHD - continuous
Social Behavior Questionnaire (SBQ)	The SBQ is designed to test for multiple psychopathologies (Murray, Eisner and Ribeaud, 2017). It has four subscales: 1) Hyperactive-impulsive 2) Inattentive 3) Aggressive	Faleschini 2020	Hyperactivity-impulsivity	ADHD – continuous

Tool	Details including Subscales	Used in the following studies	Scale / Subscales extracted	Meta analysis study is included in:
	4) Anxious-depressive Children with behavioural problems are likely to have higher scores on the SBQ (Faleschini, Matte-Gagné, Côté et al., 2020).			
The Early Child Behavior Questionnaire (ECBQ) -	The ECBQ is a "temperament" questionnaire. There are 18 subscales. Voight et al present three subscales: 1) Inhibition 2) Attention Shifting 3) Attention Focusing Attention focusing had the highest internal validity. Unlike CBLCL, Conner's and the SBQ, lower scores are abnormal (Voigt, Brandl, Pietz et al., 2013).	Voigt 2012	Attention Focusing	ADHD – continuous
Intelligence and Development Scales (IDS)	Unlike the other tests, this was not a questionnaire, but rather administered by a researcher. The IDS is a 'toolkit', designed to test for assessing social-emotional abilities. Four subtests were carried out: 1) Emotion Recognition 2) Emotion Regulation 3) Understanding of Social Situations 4) Social Behavioural Competence (Marotta et al., 2020)	Marotta 2020	Social Behavioural Competence	Social problems
			Emotion Regulation	Internalising problems
Infant Toddler Social and Emotional Assessment (ITSEA)	The ITSEA is questionnaire to be completed by primary caregivers. There are four domains: 1) externalizing behavior problems, 2) internalizing behavior problems, 3) dysregulation, 4) social-emotional competence. Mean scores ≥ 90th percentile meant a child was "at risk" of behavioural or social-emotional problems (Cheong et al., 2017).	Cheong 2017	Internalizing behavior	Internalising problems
			Externalizing behavior	Externalizing behavior
Brief Infant Toddler Social Emotional Assessment (BITSEA)	The BITSEA is a 42-item questionnaire completed by primary caregivers. There are two subscales	Johnson 2015b	Behavior problems	Global SEB problems - binary
			Delayed social competence	Social problems

Tool	Details including Subscales	Used in the following studies	Scale / Subscales extracted	Meta analysis study is included in:
	1) behavior problems (31 items). A score >25th percentile of the standardization sample classified the child as having 'behavioural problems' 2) social competence(11 items) a score <15th percentile of children of the standardization sample classified the child as having delayed social competence			
Strengths and Difficulties Questionnaire (SDQ)	The SDQ is a questionnaire completed by primary caregivers to screen for behavioural problems. There are five scales and a 'total difficulties' score: Conduct Problems Emotional Symptoms Hyperactivity Peer Problems Prosocial Behaviour (Goodman, 1997). A total score ≥17 is considered 'abnormal' (Cronin et al., 2016).	Bailhache 2022 (only completed hyperactivity and emotional symptoms scales, not full SDQ)	Emotional symptoms	Internalising disorders
			Hyperactivity scale	ADHD - binary
		Cronin 2016	"Total Difficulties"	Global SEB problems - binary
Health Status Classification System-Preschool (HSCS-PS)	This 14-item health status questionnaire, which is includes physical problems, e.g. visual or hearing problems, also has one question on 'behavioural problems'. (Klassen et al., 2004)	Klassen 2004	'Behavioural problems'	Global SEB problems - binary

Global social, emotional, and behavioural problems - binary

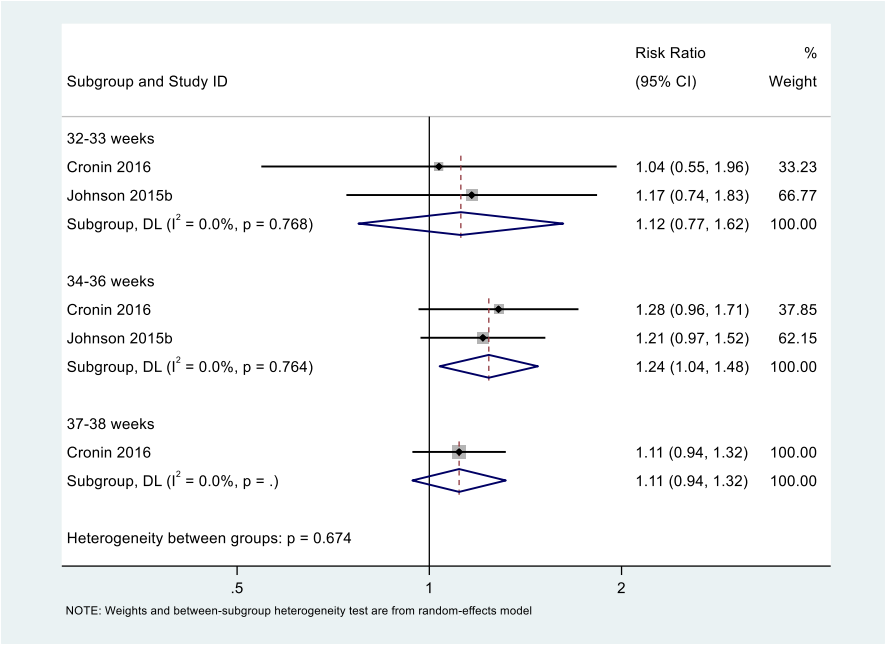


Figure 15 - Relative risk of global social, emotional, and behavioural problems by gestational age

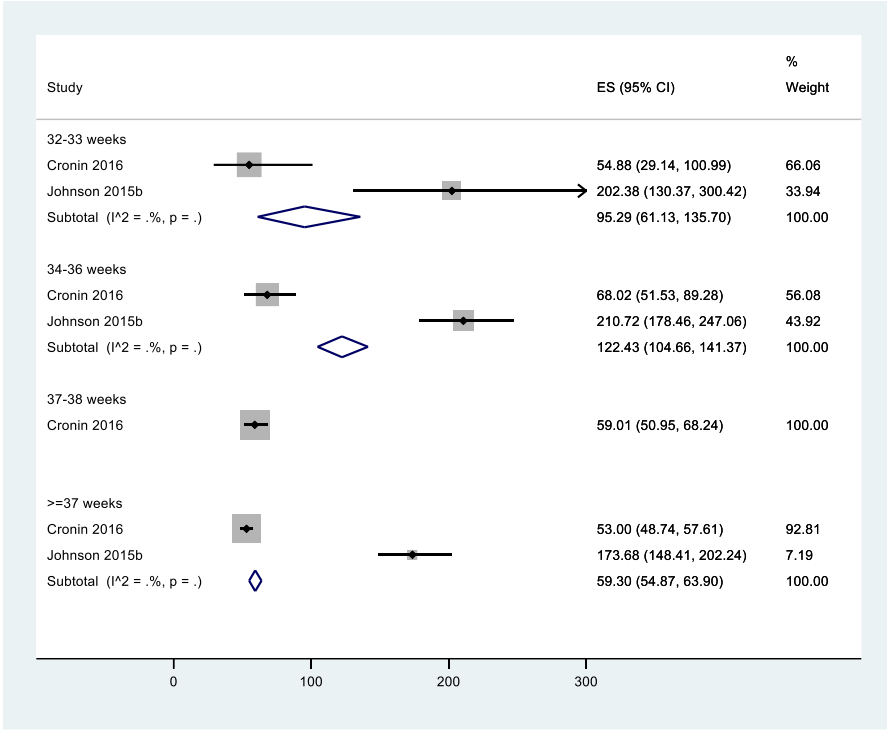


Figure 16 - Prevalence of global social, emotional, and behavioural problems by gestational age, per 1,000 children

Global social, emotional, and behavioural problems - continuous

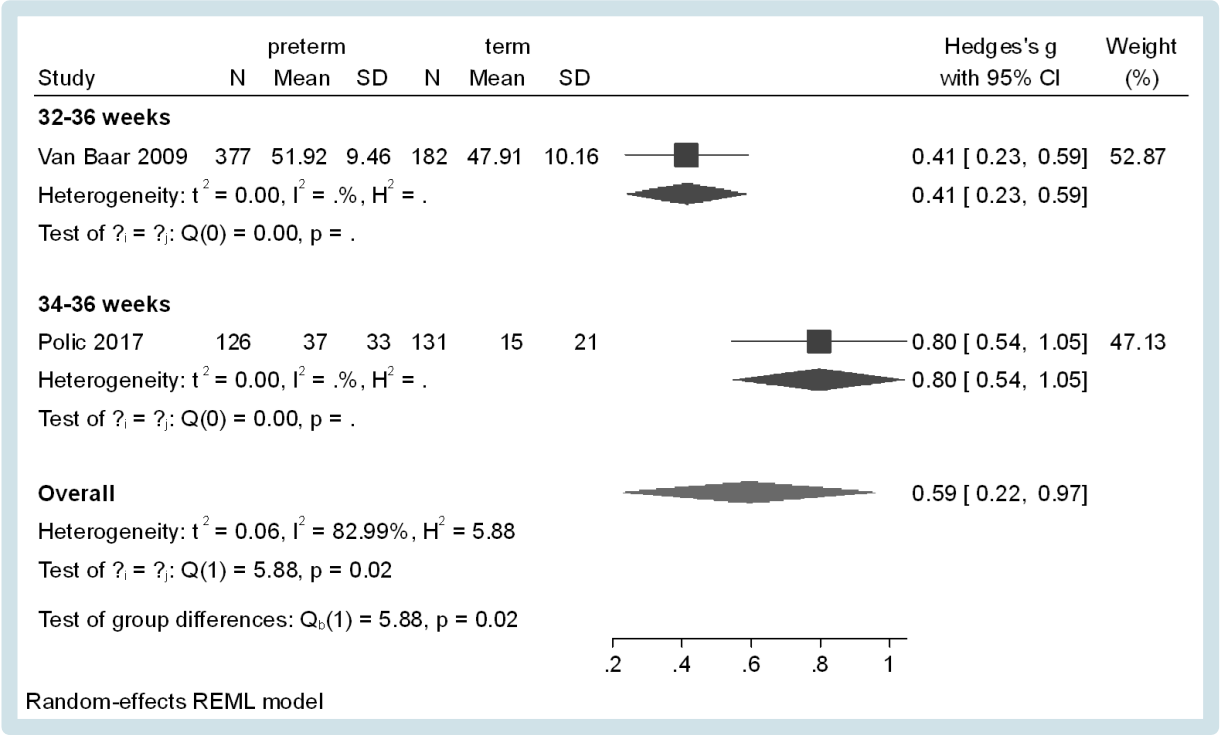


Figure 17 - Standardised mean difference of global social, emotional, and behavioural scores by gestational age (higher scores indicate increased problems)

There is increased risk of global social, emotional, behavioural problems in each group, but this is only statistically significant in the 34-36 week group (Figure 15). Global social, emotional, behavioural problems are more prevalent in all groups born before full term, except 37-38 weeks (Figure 16). The 32-33 week group's confidence intervals overlap with the term group. The standardised mean differences in social/emotional behavioural scores are higher in both preterm groups, also suggesting these children have a higher risk of difficulties in this area (Figure 17).

Internalising behaviour

The relative risk of internalising behaviour is not increased, (Figure 18) and although the prevalence in both 32-36 week and 34-36 week groups is increased (Figure 19), the confidence intervals overlap with the term group.

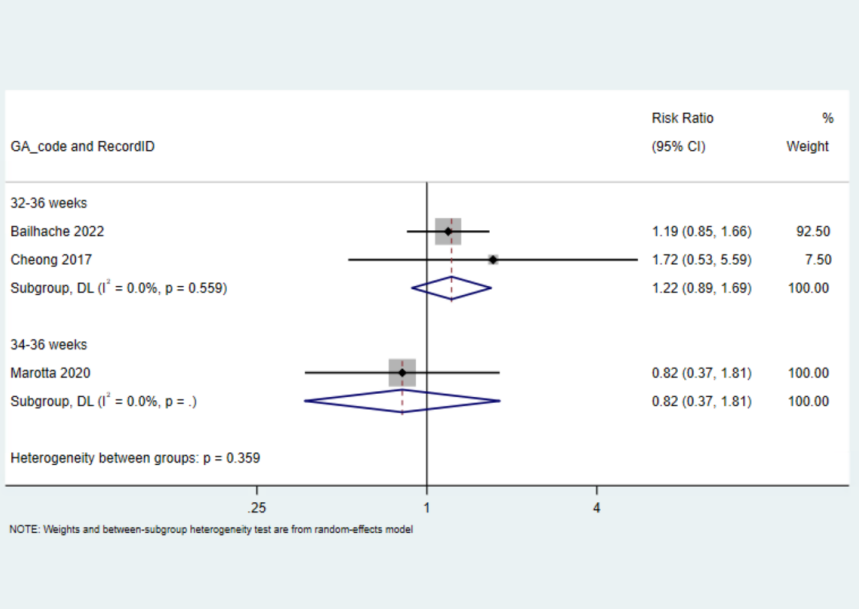


Figure 18- Relative risk of internalising behaviours by gestational age

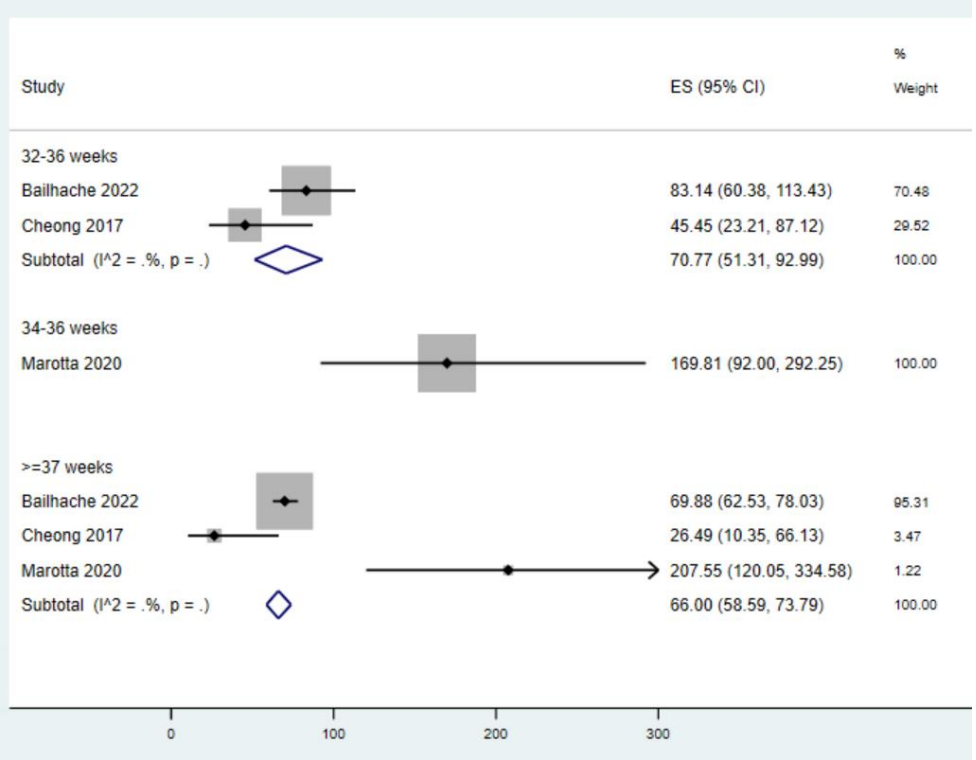


Figure 19 - Prevalence of internalising behaviours by gestational age, per 1,000 children

Externalising behaviour

There is only one study in this meta-analysis. It shows a non-statistically significant increased risk of externalising disorders in children born 32-36 weeks (Figure 20). The prevalence is also higher in the 32-36 weekers compared to the children born at term (Figure 21), although the confidence intervals overlap.

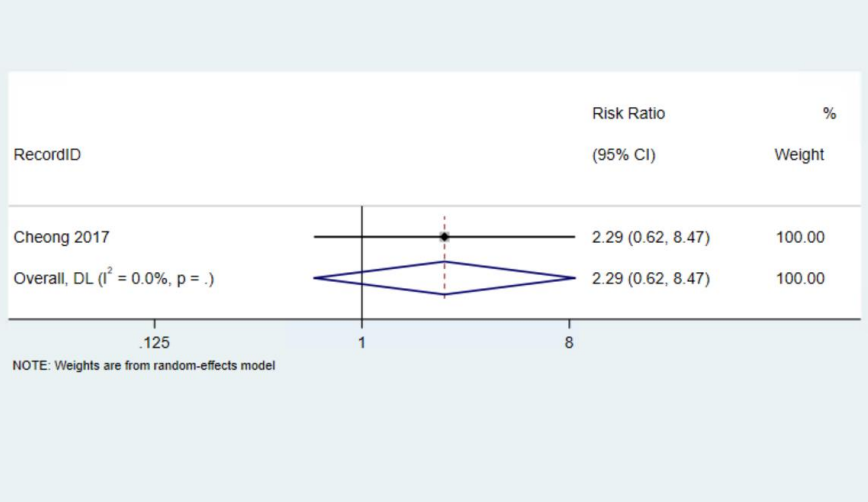


Figure 20 - Relative risk of externalising behaviour by gestational age

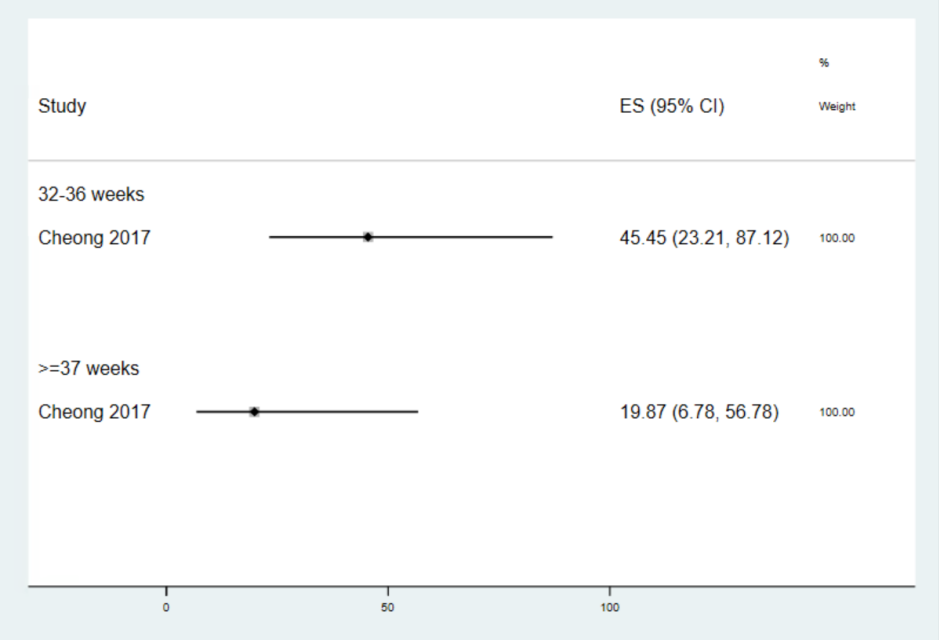


Figure 21 - Prevalence of externalising behaviour by gestational age, per 1,000 children

Social problems

There is a small increased relative risk of social problems in each gestational age group born before full term (Figure 22). In both the 32-33 week and 34-36 week groups there is an increased prevalence of social problems (Figure 23). There is no data for children born 37-38 weeks.

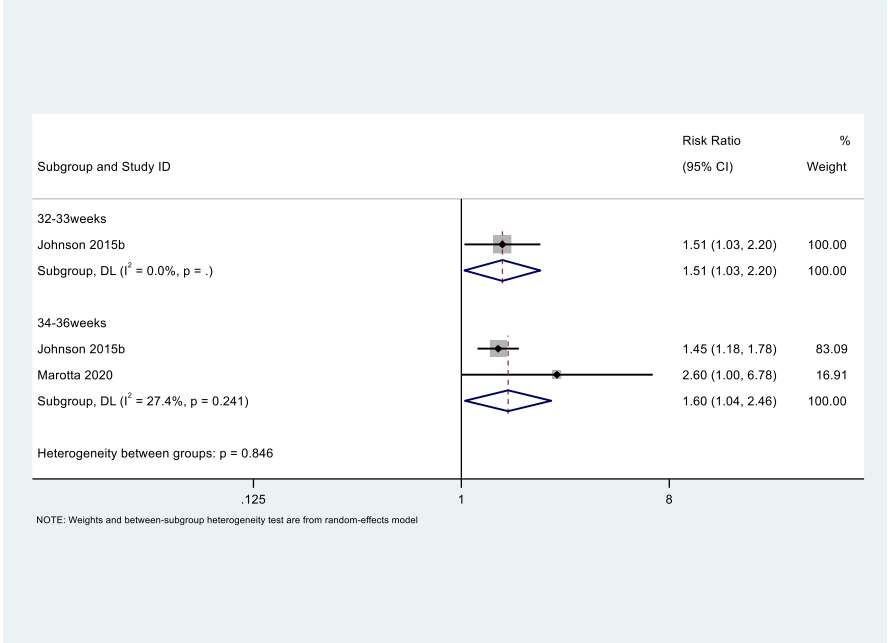


Figure 22 - Relative risk of social problems by gestational age

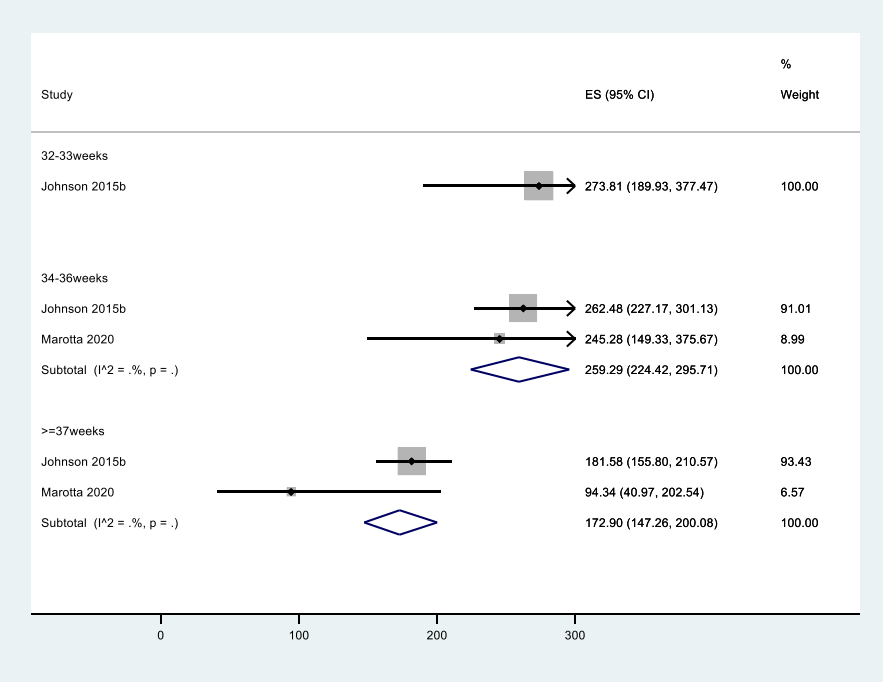


Figure 23 - Prevalence of social problems by gestational age, per 1,000 children

Hyperactivity, impulsivity, inattention, and Attention Deficit Hyperactivity Disorder (ADHD)

Eleven studies explored hyperactivity, impulsivity, inattention, or attention deficit hyperactivity disorder as an outcome (Table 13). Relative risk was calculated in two separate meta-analyses, one for binary measures of hyperactivity, impulsivity, inattention symptoms and one for continuous outcomes (Figure 24 and Figure 26 respectively). There were 25,058 children in the continuous outcome meta-analysis, from a total of seven studies, and 1,522,671 children in the binary meta-analysis, from a total of five studies. The relative risk of hyperactivity, impulsivity, inattention, or ADHD is increased in all groups born before full term. The prevalence was higher in all groups born before full term (Figure 25). The standardised mean difference was increased in all groups born before full term, but only statistically significant in the 34 – 36 week group (Figure 26), and the effect size was small (Andrade, 2020).

Table 13 - Studies reporting attention deficit hyperactivity disorder (ADHD) by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% diff. between gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Subscale extracted for meta-analysis	Study Quality
(Ask, Gustavson, Ystrom et al., 2018)	Norway	34-36 weeks: 1,755 37-38 weeks: 6,732 40 weeks: 11,753	5 years	1999 - 2008	51.3%	Not reported (NR)	Conner's Parent Rating Scale–Revised (CPRS-R:S)	12 items which reflect ADHD criteria in DSM-IV	good
(Bailhache et al., 2022)	France	32-36 weeks: 421 ≥37 weeks: 4164	9 years	2011	50.9%	NR	Strengths and Difficulties Questionnaire (SDQ)	hyperactivity/ inattention	good
(Beer, Cnattingius, Susser et al., 2022)	Sweden	37– 41 weeks: 1,071,729 32– 36 weeks: 47,859	3-15 years	2002-2014	NR	NR	ADHD diagnosis in linked records, or prescription of medication for ADHD	NA	good
(Bul and van Baar, 2012)	Netherlands	32-36 weeks: 348 ≥37 weeks: 182	8 years	1996-1999	32-36 weeks: 51.1%, ≥37 weeks: 47.8%	NR	Child Behaviour Checklist (CBCL)	ADHD subscale	good
(Crockett, Ruth, Heaman et al., 2022)	USA	34-36 weeks: 2,088 39-41 weeks: 26,012	Up to age 8	2000 - 2005	34-36 weeks: 53.6% 39–41 weeks: 51.1%	NR	ADHD in linked records, or prescription of ADHD medication	NA	good
(Faleschini et al., 2020)	Canada	32-36 weeks: 89 ≥37 weeks: 1841	4 years	1997-1998	32-36 weeks: 52% ≥37 weeks: 50%	Born in Canada 87%	Social Behavior Questionnaire (SBQ)	Hyperactivity-impulsivity	good
(Higa Diez, Yorifuji, Kado et al., 2016)	Japan	34-36 weeks: 645 37-38 weeks: 5,103 39-41 weeks: 11,752	8 years	2001	34-36 weeks 60.1% 37-38 weeks 55.3% 39-41 weeks 49.7%	NR	Child Behaviour Checklist (CBCL)	Attentional problems	good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% diff. between gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Subscale extracted for meta-analysis	Study Quality
(Lingasubramanian, Corman, Noonan et al., 2022)	USA	37-38 weeks: 400 39-41 weeks: 1,022	9 years	1998- 2000	52%	Non-Hispanic White 22%; Non-Hispanic Black 48%; Hispanic 27%; Other non-White 4%	Conners Teacher Rating Scale–Revised Short Form	ADHD index	good
(Talge et al., 2012)	USA	3-5 years: 34-36 wks: 96 ≥37 weeks: 388 6-9 years: 34-36 wks: 56 ≥37 weeks: 222	3-5 years and 6-9 years	1998–2004	48%	White/Other: 76% African American 24%	Conners' Parent Rating Scales-Revised Short Form	ADHD index	good
(Tso, Ho, Coghill et al., 2022)	Hong Kong	33-36 weeks: 22,811 37-41 weeks: 330,087	6–17 years, mean 11	2004 - 2014	52%	NR	ADHD diagnosis in linked records, or prescription of medication for ADHD	NA	good
(Voigt, Pietz, Pauen et al., 2012)	Germany	32-37 weeks: 88 ≥38 weeks: 86	2 years (corrected)	2007-2008	32-37 weeks 51%, ≥38 weeks 47%	NR	The Early Child Behavior Questionnaire (ECBQ)	Attention Focusing	fair

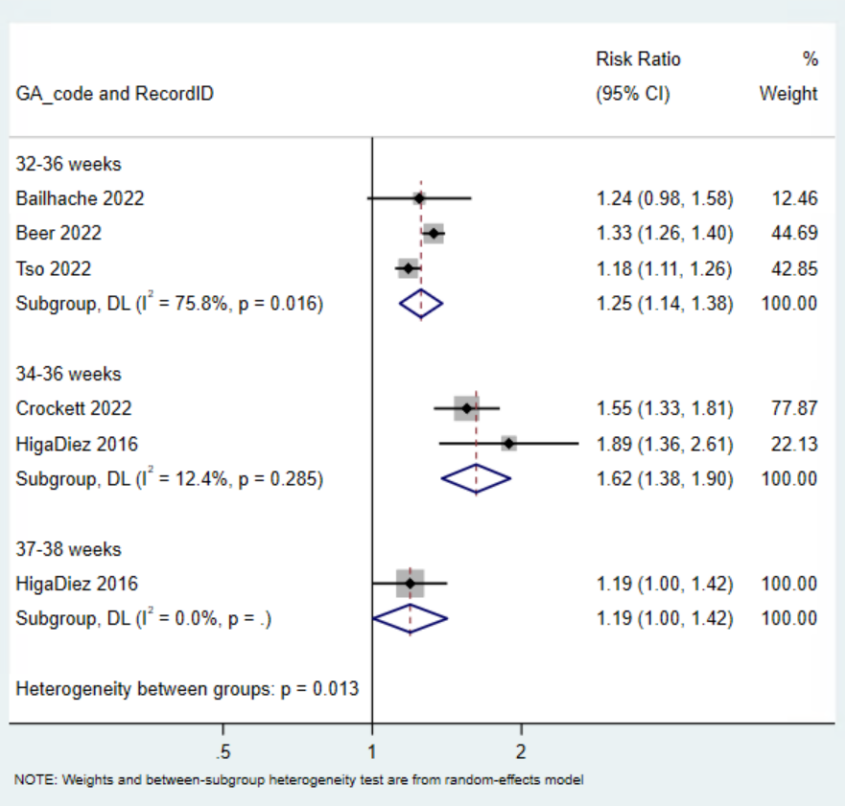


Figure 24 - Relative risk of ADHD or ADHD signs/symptoms by gestational age

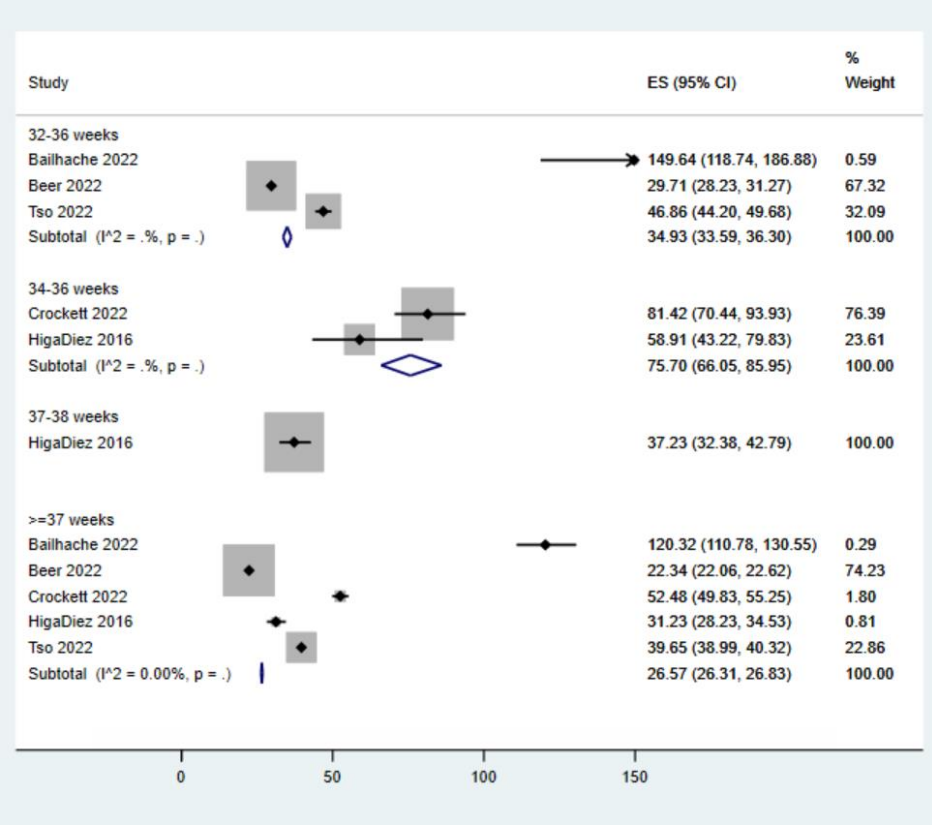


Figure 25 - Prevalence of ADHD or ADHD signs/symptoms by gestational age, per 1,000 children

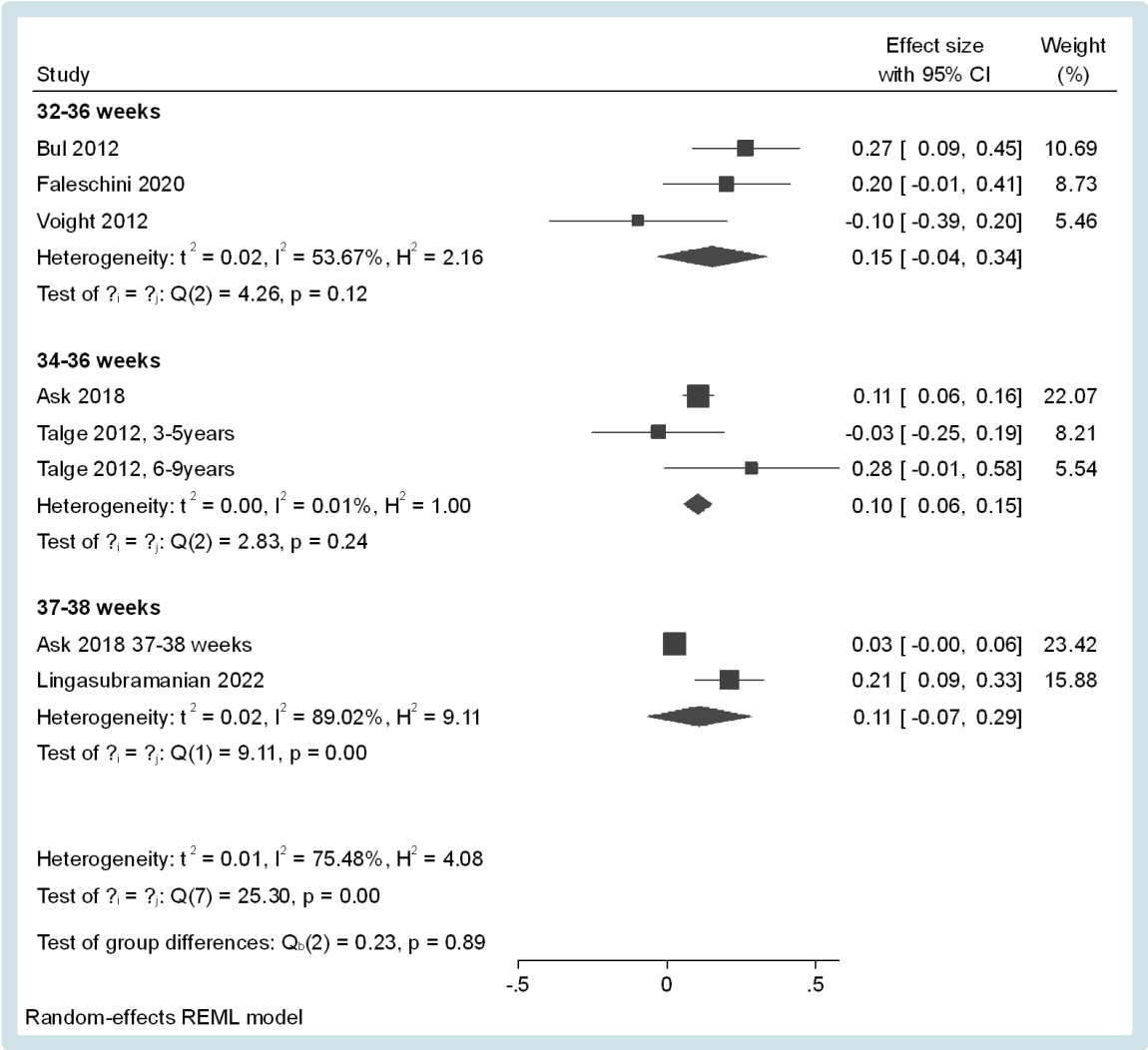


Figure 26 - Standardised mean difference of ADHD symptom scores by gestational age (higher scores indicate increased problems)

Autism Spectrum Disorder (ASD)

There was a total of 403,699 children included in this meta-analysis from three studies (Table 14). There were four studies which reported ASD as an outcome, but You (2019a) was excluded from the meta-analysis because it reported numbers of children who had 'screened' positive for ASD, but a diagnosis was not established, whereas the other three studies only included children with a formal diagnosis. Guy 2015 used the same screening test as You (2019a) (the Modified Checklist for Autism in Toddlers, M-CHAT), but when a child screened positive, they were formally assessed as to whether a diagnosis should be made. Kuzniewicz (2014) and Leavey (2013) both used linked records. The double asinine transformation caused an improbably low pooled prevalence in the 32-33 week group (lower than either of the studies reporting outcomes at 32-33 weeks) and so the *ftt* command was removed.

There seems to be a higher risk of ASD in the preterm children (Figure 27). This was not seen at 37-38 weeks (although outcomes for children born 37-38 weeks were only reported by Leavey (2013)). ASD is more prevalent in the 34-36 week group compared to the term group. The lowest prevalence is amongst the 32-33 week group (Figure 28), although the confidence intervals here are very wide, so this is most likely due to the study size.

Table 14 - Studies reporting Autism Spectrum Disorder (ASD) by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / Criteria used	Study Quality
(Kuzniewicz, Wi, Qian et al., 2014)	USA	34 - 36 weeks: 11,945 ≥ 37 weeks: 177,129	minimum 2 years	2000-2007	unclear	White: 42% Hispanic: 24% Asian: 21% Black 7% Other 6%	ASD diagnosis in medical records	good
(Leavey, Zwaigenbaum, Heavner et al., 2013)	Canada	32 - 33 weeks: 2,373 34-36 weeks: 13,108 37-38 weeks: 51,307 39-41 wks: 146,467	minimum 3 years	1998-2004	49%	Not reported (NR)	ASD diagnosis in medical records	good
(Guy et al., 2015)	UK	32 - 33 weeks: 82 34 - 36 weeks: 539 ≥ 37 weeks: 749	2 years corrected	2009-2010	NR	98% white in the group with a negative ASD screen	ASD on M-CHAT then follow-up interview to identify true positives	fair
(You et al., 2019a)	China	Not included in MA	2 years	2013 -2015	34-36weeks: 54.5%, 37–42 weeks: 47.5%	NR	M-CHAT	fair

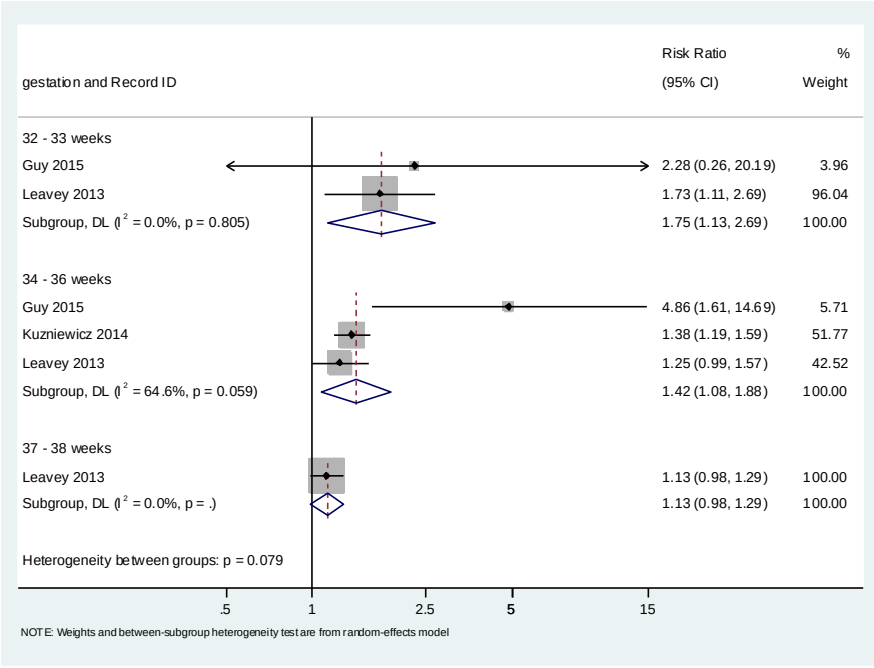


Figure 27 – Relative risk of ASD by gestational age

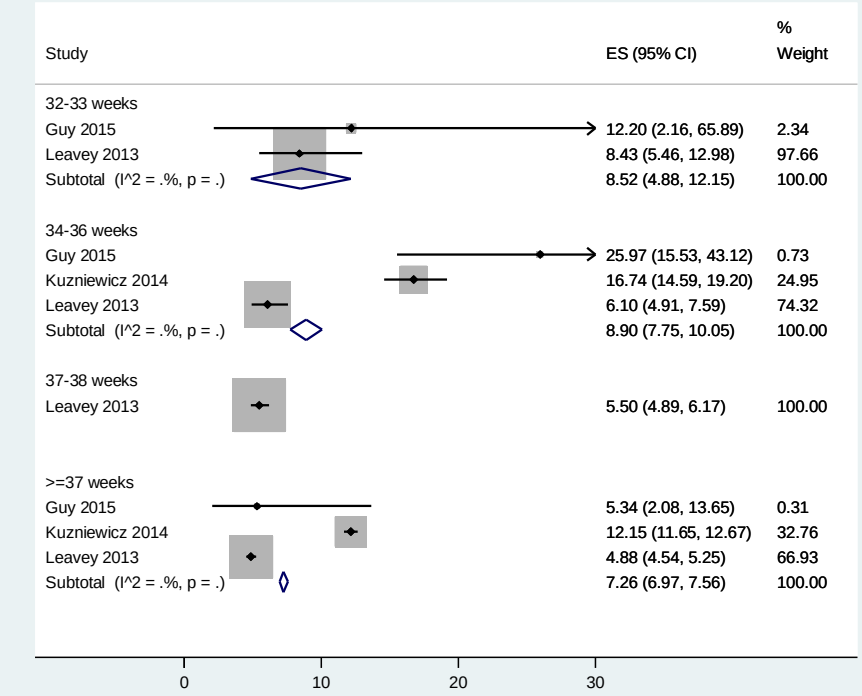


Figure 28 - Prevalence of ASD by gestational age, per 1,000 children

Developmental Delay

In order to enable meaningful comparisons, four subgroups of developmental delay were investigated: global developmental delay, cognitive delay, motor delay (which includes fine and gross motor skills and can also be called 'physical development'), and language delay, see Table 15. Whilst defining domains of development is challenging, and there is no definitive consensus (Bedford, Walton and Ahn, 2013), the domains presented here are consistent with those typically used in clinical practice (Rydz, Shevell, Majnemer et al., 2005).

Making a distinction between cognitive impairment as opposed to cognitive delay (as a subtype of developmental delay) is somewhat arbitrary. The children included in the cognitive delay meta-analysis were mainly assessed at 2 years old (3/4 studies) and mainly used the Bayley's scale (3/4 studies), whereas the children in the cognitive impairment meta-analysis tended to be older, and many had a formal diagnosis of cognitive impairment.

There was a total of 472,137 children included in the global developmental delay meta-analysis; 9,044 children in the motor delay meta-analysis; 40,799 in the language delay meta-analysis; and 8,505 children in the cognitive delay meta-analysis.

Zambrana (2021) presented results from a regression analysis, and it was unclear how many children were in each subgroup; therefore, it could not be included in the prevalence meta-analysis. Potijk (2013), Kerstjens (2011), and Kerstjens (2012) all used the Longitudinal Preterm Outcome Project (LoliPOP) cohort data, which had already been included via Hornman (2017), although the results of Hornman (2017) and Zhou (2020) were not presented, as they were only presented as 32-36 weeks, which as per methods were not displayed as there were already 32-33 week and 34-36 week groups. Beauregard (2018a), Richards (2016), Nepomnyaschy (2012), Shah (2016a) and Woythaler (2011) all used data from the Early Childhood Longitudinal Studies Program Birth cohort (ECLS-B); Woythaler (2011) was included in the meta-analysis even though it was an older publication because it presented the results as a binary outcome that was simple to extract and would allow the calculation of prevalence. You (2019a) presented motor delay and global delay. This was meta-analysed in the motor delay section only, as the prevalence of global developmental delay in their cohort seemed improbably high.

Chen (2014) reported language problems, but as with the social, emotional, and behavioural problems above, only the results of the regression were presented, and it was unclear exactly how many children were in each group. The authors were contacted but did not respond. Kern (2007) presented the data according to whether or not the child was first or second born but did not state how many in each gestational age category were first or second born which made it impossible to meta-analyse. The authors found that lower gestational ages were related to vocabulary size and grammatical distribution.

Global developmental delay is associated with gestational age; the risk of global developmental delay is increased in all groups born before full term (Figure 29). The same picture is seen with prevalence of global developmental delay which is increased in 32-33 weeks, 34-36 weeks, and 37-38 weeks (Figure 30). The results of this meta-analysis were largely driven by Curry (2012) which was larger than the other studies. Of note is the much lower prevalence demonstrated by Petrini (2009), likely reflecting the different outcome measure.

The risk of motor delay is not significantly increased in either group born before term (Figure 31). The prevalence meta-analysis which shows a substantially increased prevalence of motor delay in the 32-36 week children, but this is not seen in the 34-36 week group, where the prevalence was very similar to the term group (Figure 32).

The meta-analysis of the papers reporting language development delay show the risk is increased in in all the groups born 32-38 weeks, although the effect size is small and is largely driven by a single study (Stene-Larsen (2014)) and is only statistically significant in the 34-36 week group (Figure 33). Also, note that Klassen (2004) is an unusual study since all the term children in this sample had been admitted to NICU, which likely accounts for the much higher prevalence in their term comparator group (Figure 34).

There is an increased risk of cognitive developmental delay in the 32-26 week and 34-36 week group Figure 35. Despite this, the prevalence is not straightforward; it appears that the prevalence of cognitive delay is higher in the term group than in the 32-36 week group (Figure 36). This is because Woythaler (2011) has a high prevalence of cognitive developmental delay which brings up the pooled prevalence in the term group, but it is not included in the 32-36 week group. Darlow (2009) shows the 32-36 week group has a reduced risk of cognitive developmental delay, but the comparison group here were all admitted to neonatal intensive care, and therefore not a typical control group.

Table 15 - Studies reporting developmental delay by gestational age. DD: developmental delay

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between different gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria for meta-analysis	Meta-analysis included in	Study Quality
(Beauregard, Drews-Botsch, Sales et al., 2018a)	USA	Children from cohort already included in MA	5 years	2001	50.8%	White: 42% Black: 18%, Hispanic: 17%, Asian: 10%,			Good
(Cheong et al., 2017)	Australia	32-36 weeks: 194 ≥37 weeks: 177 (Motor DD) 32-36 weeks: 190 ≥37 weeks: 178 (Language DD) 32-36 weeks: 197 ≥37 weeks: 181 (cognitive DD)	2 years	2009-2012	32-36 weeks: 47.8% ≥37 weeks: 53.2 %	Not reported (NR)	Bayley Scales of Infant and Toddler Development -III	Motor DD Language DD Cognitive DD	Good
(Curry, Pfeiffer, Slopen et al., 2012)	USA	32–33 weeks: 3,973 34–36 weeks: 21,835 37–38 weeks: 79,228 ≥39 weeks: 229,626	up to 3 years	1999 - 2001	Whole cohort 51.3% (not reported by gestation)	Hispanic 34.3%. Asian/Pacific Islander 11.9%. Black, non-Hispanic 27.6%. White, non-Hispanic 25.9%, Other 0.2%	Referral to early intervention programme	Global DD	Good
(Darlow, Horwood, Wynn-Williams et al., 2009)	New Zealand	33–36 weeks: 112 ≥37 weeks: 101	2 years	2001-2002	33-36 weeks: 61% Term admissions 59%	Māori 5.9%	Bayley Scales of Infant and Toddler Development -II	Motor DD, Cognitive DD	Good
(de Jong et al., 2015)	Netherlands	32-36 weeks: 116 37-41 weeks: 98	4 years	2010-2011	32-36 weeks 57.8% >37 weeks: 45.5%	Dutch 95.9%	Bayley-III	Motor DD, Language DD,	fair

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between different gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria for meta-analysis	Meta-analysis included in	Study Quality
								Cognitive DD	
(Demestre, Schonhaut, Morillas et al., 2016)	Spain	34-36 weeks: 90 38-41 weeks: 89	4 years	2009	34-36 weeks: 61% 38-41 weeks: 55%	NR	Ages and Stages Questionnaire	Global DD	good
(Hornman, de Winter, Kerstjens et al., 2017)	The Netherlands	Excluded from MA, only presented 32-36 week group	4 years	2002-2003	34-36 weeks: 58.3% 38-41 weeks: 47.1%	Non-Dutch background 4.3%	Ages and Stages Questionnaire	Global DD	good
(Kern and Gayraud, 2007)	France	Unable to extract data	2 years	unclear	Preterm 55.0% Term 52.0%	NR			fair
(Klassen et al., 2004)	Canada	33-37 weeks: 339 >37 weeks: 255	3.5 years	1996-1997	33-37 weeks: 45.2% >37 weeks: 40.2%	NR	Health Status Classification System Preschool Version	Language DD	fair
(Kerstjens, de Winter, Bocca-Tjeertes et al., 2011)	Netherlands	Data already included	3.5 - 4 years	2002-2003	32-35 weeks: 57.4% 38-41 weeks: 49.6%	Mother born within Netherlands 95.6%			good
(Kerstjens, AF, Bocca-Tjeertes et al., 2012)	Netherlands	Data already included	4 years	2002-2003	53.7%	Dutch 94.9%			good
(Nepomnyaschy, Hegyi, Ostfeld et al., 2012)	USA	34–36 weeks: 625 37-41 weeks: 5,000	2 years	2001	NR	White non-Hispanic: 61% Black, non-Hispanic: 13% Hispanic: 21% Other: 4%	The Bayley Short Form Research Edition	cognition	good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between different gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria for meta-analysis	Meta-analysis included in	Study Quality
(Patil and Metgud, 2014)	India	32-36 weeks: 100 ≥37 weeks: 100	4-6 years	unclear	Preterm 59% Term 61 %	NR	FirstSTEP Screening Test for Evaluating Pre-schoolers	Motor DD, Language DD, Cognitive DD	fair
(Petrini et al., 2009)	USA	34-36 weeks: 8,341 37-41weeks: 128,955	1 - 5 years	2000 - 2004	34-36 weeks: 54.4% 37-41 weeks: 50.9%	Hispanic: 24.5%, Asian: 18.2%, White: 41.5%, Unknown: 8.5%, Black: 7.3%,	Developmental delay / "Mental retardation" - ICD-9 codes	Global DD	good
(Perez-Pereira, Fernandez, Gomez-Taibo et al., 2014)	Spain	Only study reporting continuous outcomes	2.5 years	unclear	34-36 weeks: 56.5%, ≥ 37 weeks: 51.4%	NR			fair
(Richards, Drews-Botsch, Sales et al., 2016a)	USA	Data already included	4-5 years	2001	51% (not reported by gestation)	White, non-Hispanic 43.3%. Black or African American 17.8%. Hispanic 17.4%; Asian 9.1%. More than 1 race, non-Hispanic 8.8% Pacific Islander 0.5%; American Indian or Alaska Native 2.9%; Missing 0.2%			good
(Shah, Kaciroti, Richards et al., 2016a)	USA	Data already included	2 years	2001	34-36 weeks: 49.5% 37-38 weeks: 50.9% 39-41 weeks: 50.5%	White 58.5%; Hispanic 22.5%. Black 13.1%; Asian 3.5%. Other 2.3%			good
(Stene-Larsen, Brandlistuen, Lang et al., 2014)	Norway	34-36 weeks: 1,673 37-38 weeks: 7,109 39-41 weeks: 30,641	3 years	1999 - 2008	34-36 weeks: 51.3% 37-38 weeks: 48.6% 39 – 41 weeks: 50.4%	NR	Selected items from the Ages and Stages Questionnaire	Language DD	good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between different gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria for meta-analysis	Meta-analysis included in	Study Quality
(Woythaler, McCormick and Smith, 2011)	USA	34-36 weeks: 1,200 ≥37 weeks: 6,300	2 years	2001	34-36 weeks: 52.6% ≥37 weeks: 51.4%	White 81.4% Black 14.3% Other 4.3%	Bayley Short Form–Research Edn Mental development index <70	Motor DD, Cognitive DD	good
(You et al., 2019a)	China	34-36 weeks: 102 37–42 weeks: 153	24-30m	2011 - 2013	34-36 weeks: 66.7% 37–42 weeks: 61.4%	NR	falling behind 3m of milestone or development quotient<75 on Gesell Development Diagnosis Scale (GDDS)	Motor DD	good
(You et al., 2019b)	China	34-36 weeks: 112 37–42 weeks: 179	2 years	2013 - 2015	34-36weeks: 54.5%, 37–42 weeks: 47.5%	NR	development quotient <75 for gross motor skills on GDDS	Motor DD	fair
(Zhou, Qu, Yang et al., 2020)	China	Excluded from MA, only presented 32-36 week group	1m -5 years	2011-2016	32–37 weeks: 51.8% 37–42 weeks: 53.8%	NR	Ages and Stages Questionnaire	Global DD	good

Global developmental delay

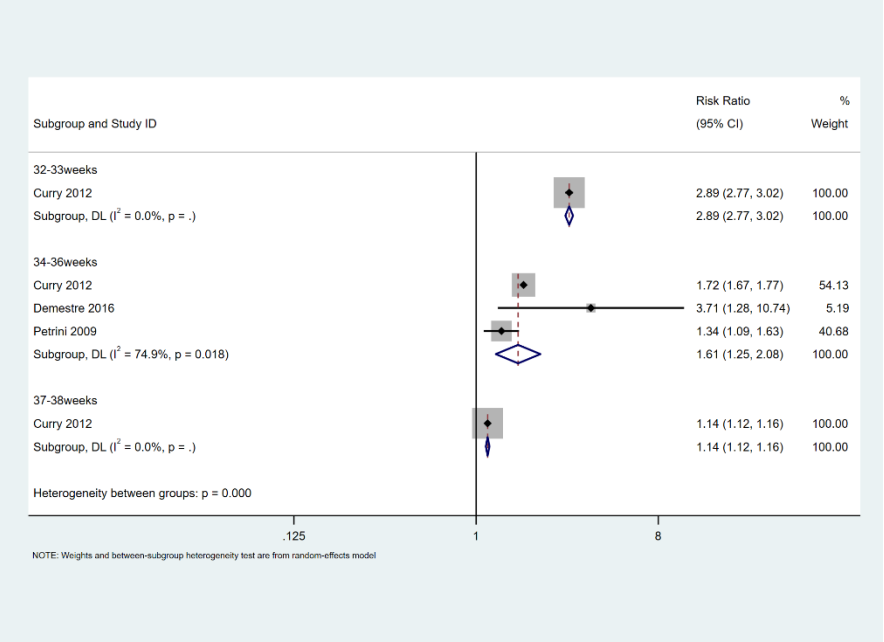


Figure 29 - Relative risk of global developmental delay by gestational age

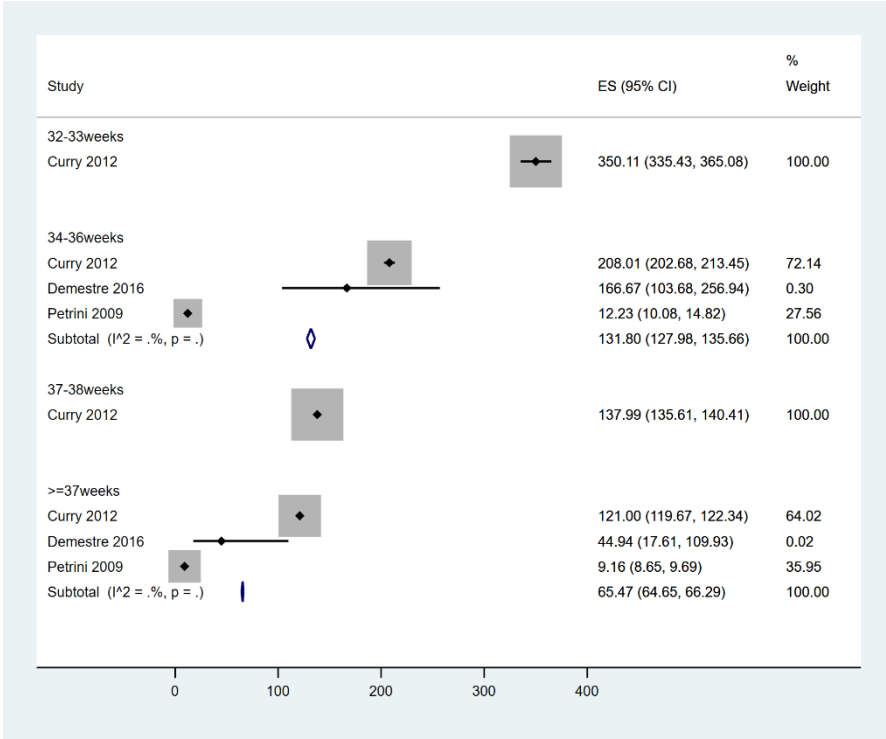


Figure 30 - Prevalence of global developmental delay by gestational age, per 1,000 children

Motor development delay

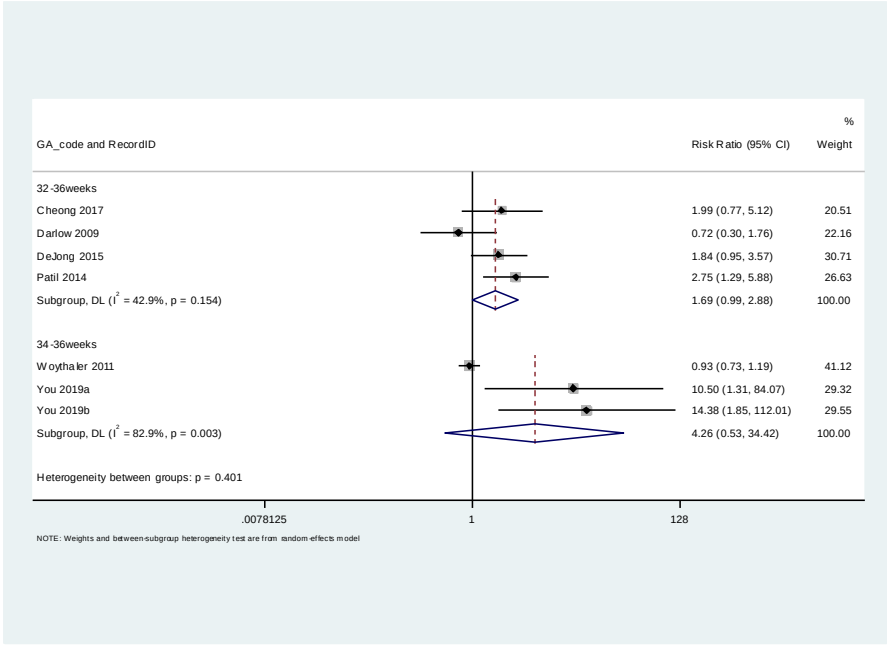


Figure 31 - Relative risk of motor developmental delay by gestational age

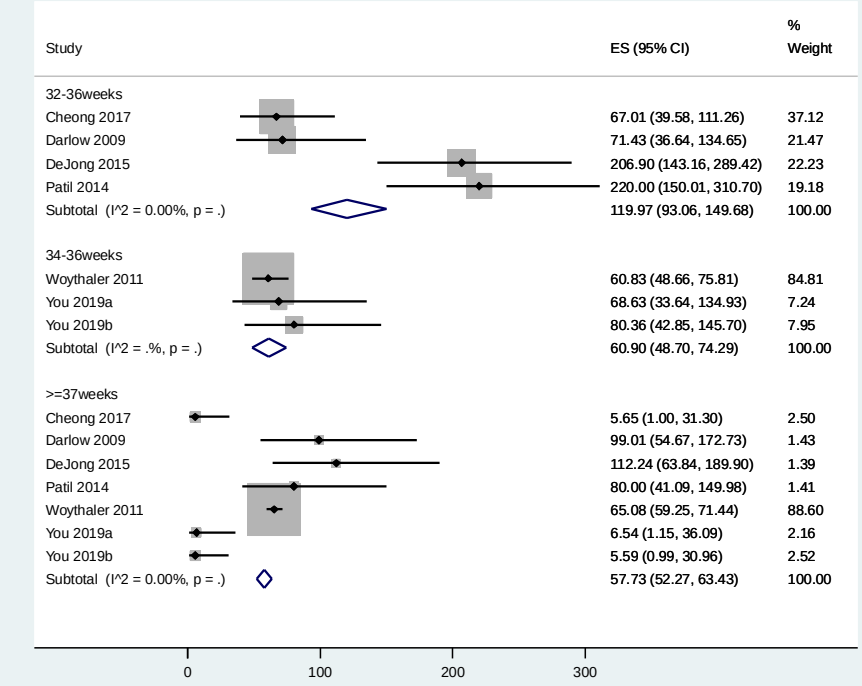


Figure 32 - Prevalence of motor developmental delay by gestational age, per 1,000 children

Language delay

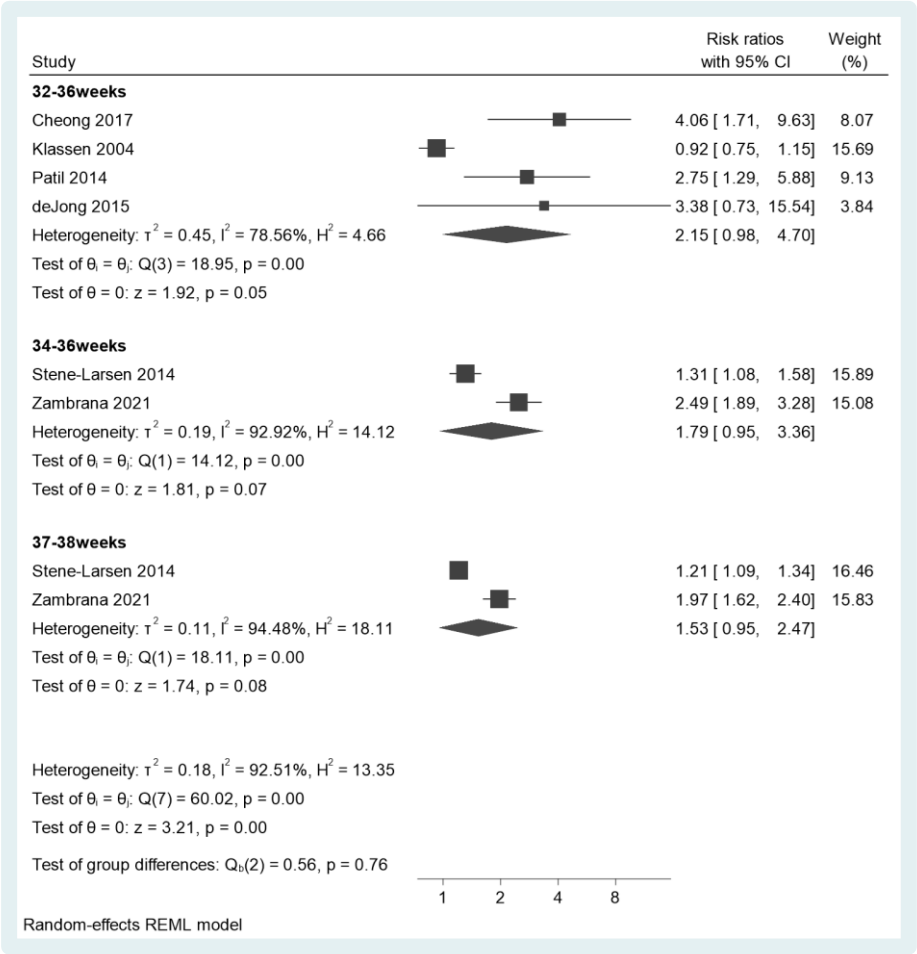


Figure 33 - Relative risk of language developmental delay by gestational age

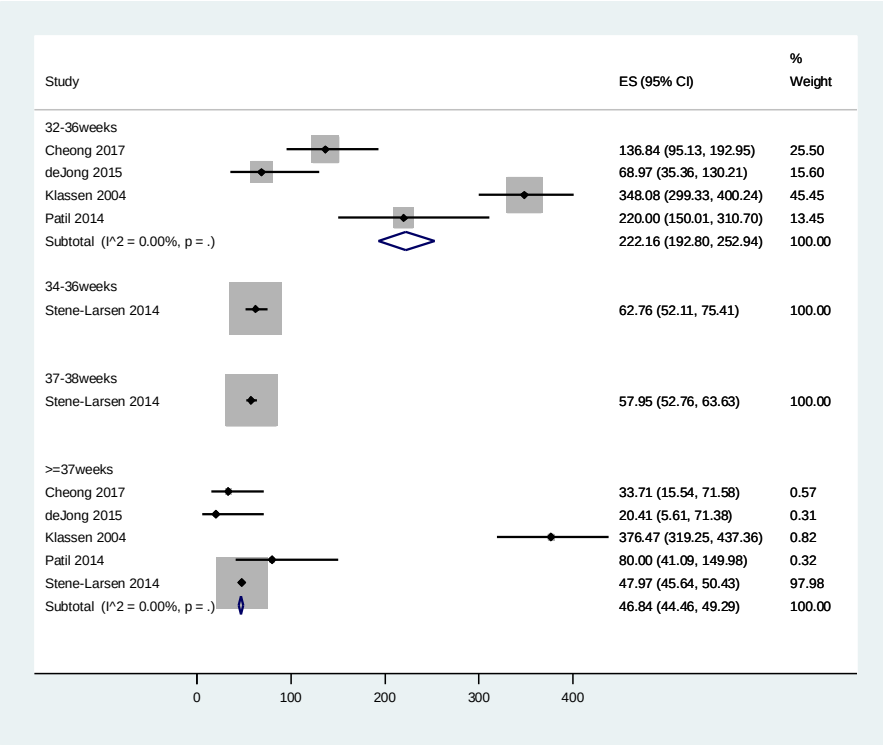


Figure 34 - Prevalence of language delay by gestational age, per 1,000 children

Cognitive development delay

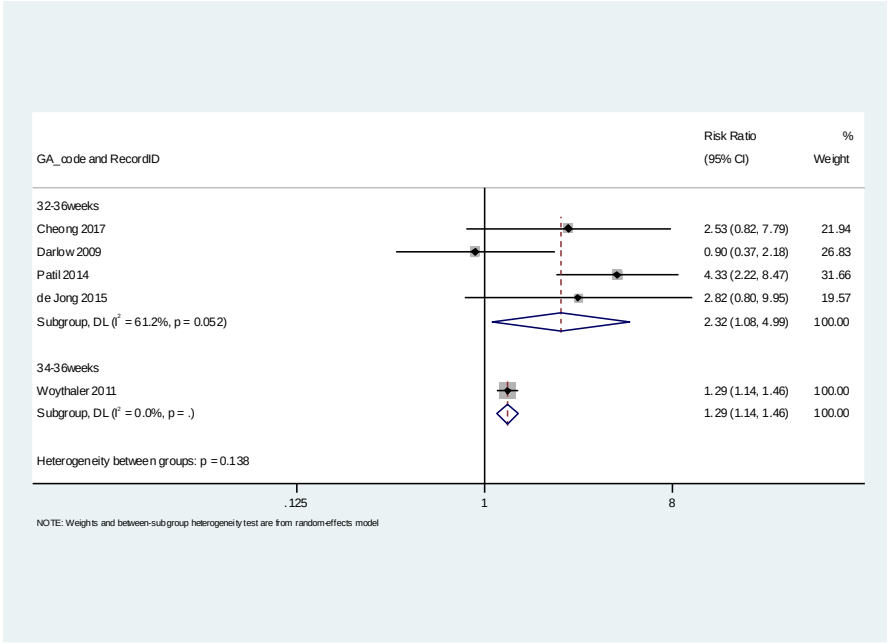


Figure 35 - Relative risk of cognitive developmental delay by gestational age

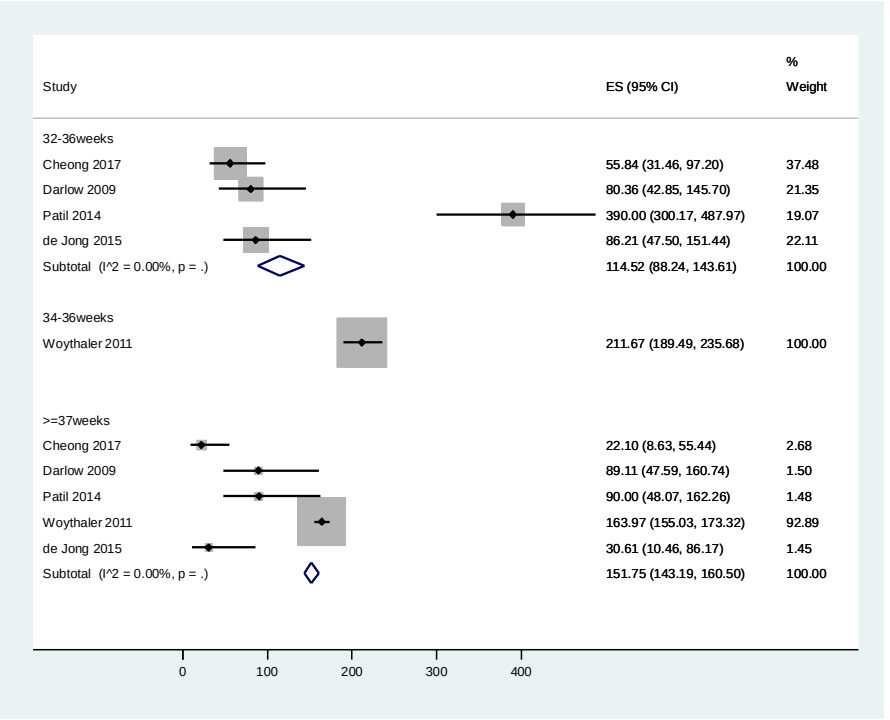


Figure 36 - Prevalence of cognitive developmental delay by gestational age, per 1,000 children

Cognitive Impairment

There were nine studies reporting cognitive impairment as a binary outcome and twelve as a continuous outcome. Three papers reporting cognitive impairment as a binary outcome could not be meta-analysed. There was a total of 677,481 from six studies in the binary outcome meta-analysis and 12,593 children from five studies included in the continuous outcome meta-analysis (Table 16 and Table 17).

Fitzpatrick (2016) and Beauregard (2018b) were not included in the meta-analysis because they used Millennium cohort study data, which was already included via Poulsen (2013), which presented the data in a form which made it easier to extract the data. Chen (2014) could not be included as the raw data was not presented, only the results of a regression analysis, but without sufficient data to enable its inclusion. Six studies were not included in the continuous outcomes meta-analysis because they only presented data for the 32-36 week group, and there was also a 32-33 week group and a 34-36 week group, therefore a 32-36 week group was not presented, as per the methods.

Making a distinction between cognitive impairment as opposed to cognitive delay (as a subtype of developmental delay) is somewhat arbitrary. The majority of the 'cognitive impairment' assessments were carried out when the children were older than when the developmental delay assessments were done; in 15/18 studies the children were over 2 years old and in 9/18 studies the children were ≥ 5 years old. The most commonly used scales were the Differential Ability Scales (4/18) and the Wechsler Intelligence Scale (3/18); whereas for the cognitive delay meta-analysis, the majority of studies used the Bayley Scales of Infant and Toddler Development. Differential Ability Scales have been shown to correlate highly with the Weschler IQ test (Elliott, 2007). No children were included in both the cognitive developmental delay and the cognitive impairment meta-analyses.

For the prevalence meta-analysis, the double arcsine transformation was not used, as it caused an improbably low pooled prevalence in the term group (lower than in any of the individual studies) so the *ftt* command was removed from the code and the resulting pooled estimate was feasible.

Cognitive impairment is more prevalent in the 32-33 week and 34-36 week children compared to 37-38 week and term children. This is largely driven by Chen (2020) which had many more participants than the other studies, and a lower prevalence (Figure 38). Note the prevalence in Chen (2020) is very different from Poulsen (2013). This is likely related to the tests used: Poulsen

(2013) tested children part of a cohort study, whereas Chen (2020) used ICD codes in linked records.

The relative risk of cognitive impairment is the same in the 32-33 week and 34-36 week groups (1.86), however it does not reach statistical significance in the 34-36 week group. The effect is also seen in the 37-38 week group, but it is small (Figure 37).

The meta-analysis of continuous outcomes shows an effect of gestational age, where scores were lower in the children born before full term, although this did not reach statistical significance in the 32-33 week group (Figure 39). The effect size was small (Andrade, 2020).

Cognitive impairment – binary outcome

Table 16 - Studies reporting cognitive impairment as a binary outcome, by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% diff. between gestational ages)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria for meta-analysis	Study Quality
(Baron, 2010 #302)	USA	35-36 weeks: 118 ≥37 weeks: 100	3 years	2004–2006	35-36 weeks: 50% ≥37 weeks: 60%	Caucasian: 72%; Multiracial: 14%; Hispanic: 6%; Asian: 4% African/African American: 3% Other: 1%	General conceptual ability on Differential Ability Scales, 2nd edn - 1 SD < mean of 100	good
(Chen et al., 2014)	Australia		4.75 years (mean)	1999, 2000, 2004	51%	Not reported (NR)		good
(Chen, Tedroff, Villamor et al., 2020)	Sweden	37-38 wks: 132,997 39-41 wks: 530,988	3 years	1998 - 2009	51.1%	NR	Clinical codes from patient register	good
(Beauregard, Drews-Botsch, Sales et al., 2018b)	UK		3 years	2000 - 2002	51%	White British: 86%; Mixed: 4%. Pakistani/Bangladeshi: 3%. Indian: 2%; Black/Black British 1%		good
(Fitzpatrick, Carter and Quigley, 2016)	UK		3,5,7 years	2000 - 2001	32- 33 weeks 62.4% 34-36 weeks: 52.8% 37 – 38 weeks: 51.7% 39 – 41 weeks: 50.2%	White 87.1% Other 12.9%		good
(Johnson et al., 2015a)	UK	32-33 weeks: 85 34–36 weeks: 545 37-42 weeks: 750	2 years corrected	2009 - 2010	32-36 weeks 53.8% Term 50.2%	White 82.5%. Asian or Asian British 11.2%. Black or Black British 4.4%. Chinese or other 1.0%. Mixed 1.0%	Parent Report of Children's Abilities-Revised score of <35	good
(Larroque et al., 2008)	France	32 weeks: 423 39-40 weeks: 320	5 years	1997	52% male	NR	Kaufman Assessment Battery - mental processing composite <85	good
(Oros, Altermir, Elia et al., 2014)	Spain	34-36 weeks: 6 ≥37 weeks: 96	6-13 years	1997-2005	34-36 weeks:40.9% Term 52.6%	Caucasian 99.3%	Bender test - any value 1 SD > mean	fair
(Poulsen, Wolke, Kurinczuk et al., 2013)	UK	32–33 weeks: 123 34–36 weeks: 646 37–38 weeks: 2,188 39–41 weeks: 8,096	3 years	2000-2002	32-33 weeks: 59.7% 39–41 weeks: 50.6%	White British: 80-89%	Selected subscales from the British Ability Scale, 2nd edn	good

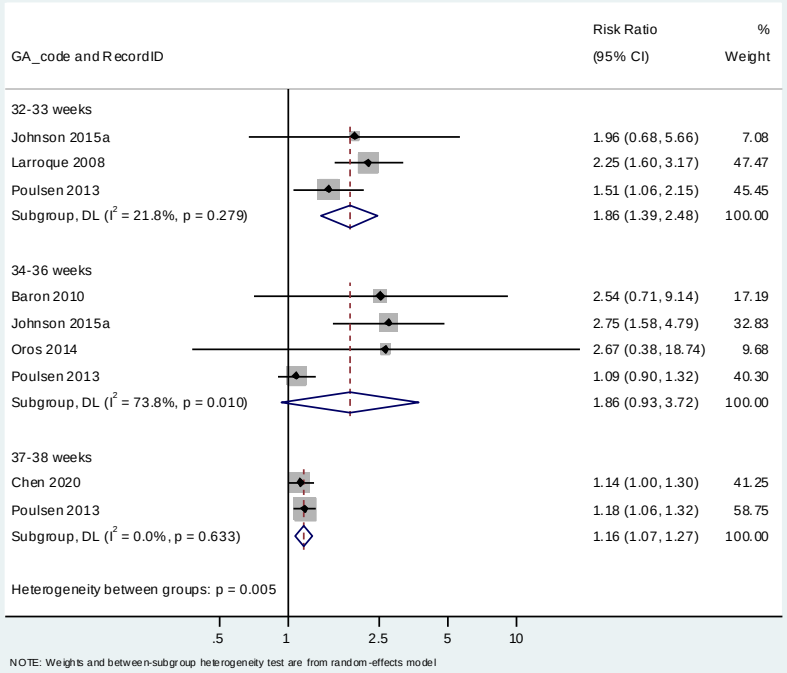


Figure 37 - Relative risk of cognitive impairment by gestational age

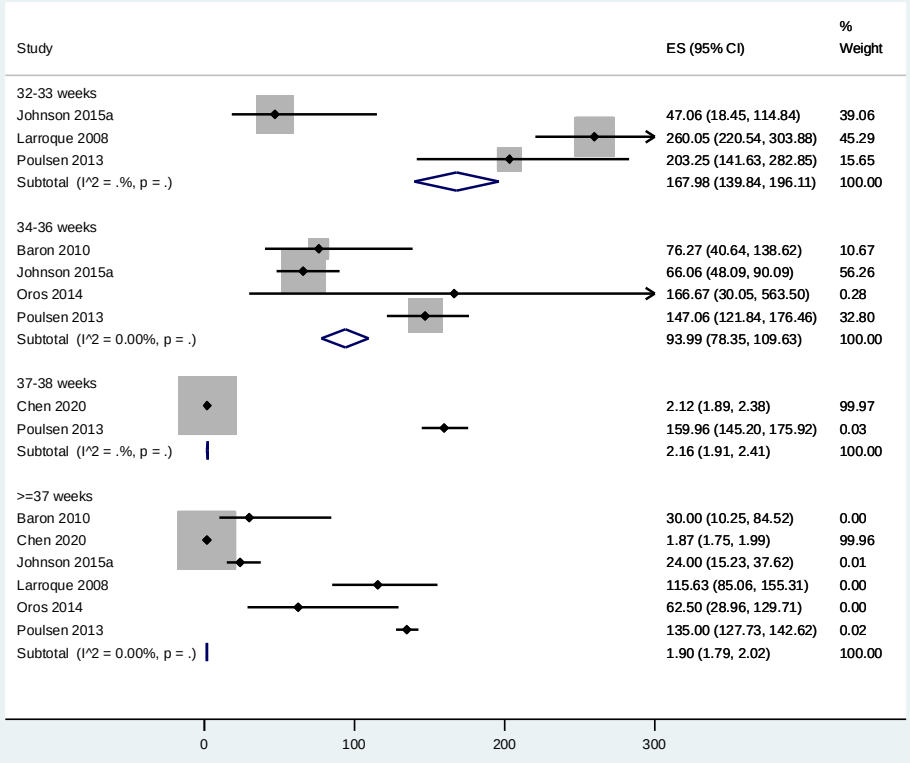


Figure 38 - Prevalence of cognitive impairment by gestational age, per 1,000 children

Cognitive impairment – continuous outcome

Table 17 - Studies reporting cognitive impairment measures by gestational age, as a continuous outcome

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% difference between gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Study Quality
(Baron, Erickson, Ahronovich et al., 2009)	USA	34-36 weeks: 60 ≥37 weeks: 35	3 years	2004-2005	34-36 weeks 45% ≥37 weeks 60%	Not reported (NR)	Differential Ability Scales-II - General Conceptual Ability	fair
(Baron et al., 2012)	USA	34-36 weeks: 52 ≥37 weeks: 195	3 years	2004 and 2006	34-36 weeks: 51% ≥37 weeks: 59%	Caucasian: 72.7%	Differential Ability Scales-II Recall of Digits	fair
(Baron, Weiss, Baker et al., 2014)	USA	34-36 weeks: 410 ≥37 weeks: 192	3 years	2004–2008	34-36 weeks: 55.4% ≥37 weeks: 53.1%	White: 67.7%; Other: 24%; Hispanic: 6.3% African American:2.1%	Differential Ability Scales	good
(Brumbaugh, Hodel and Thomas, 2014)	USA	Excluded from MA, only presented 32-36 week group	4 years	2005 - 2006	32-34 weeks:59% 38-42 weeks: 50%	NR	Peabody Picture Vocabulary Test-4	fair
(Cserjesi, Van Braeckel, Butcher et al., 2012)	The Netherlands	Excluded from MA, only presented 32-36 week group	6.9 years (mean)	2002-2003	32–36 weeks: 55.6% 38–41 weeks: 44.6%	NR	Wechsler Intelligence Scale, 3rd Edition	good
(Hodel, Brumbaugh, Morris et al., 2016)	USA	Excluded from MA, only presented 32-36 week group	4.5 years	not stated	32–36 weeks: 51.1% 37-42 weeks: 54.3%	Caucasian 92%	subtests of the Wechsler Preschool and Primary Scale of Intelligence-III	fair
(Perez-Pereira,	Spain	32-33weeks: 31 34 - 36 weeks: 42	5 years	unclear	52%	NR	Batelle Developmental	good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% difference between gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Study Quality
Fernandez, Gomez-Taibo et al., 2020)		≥37 weeks: 33					inventory cognitive score	
(Reuner, Weinschenk, Pauen et al., 2015)	Germany	Excluded from MA, only presented 32-36 week group	2 years	2008-2009	33–36 weeks: 50% ≥37 weeks: 47%	NR	Mental Scale of the Bayley Scales, 2nd edition	fair
(Schneider, Burns, Giles et al., 2014)	Australia	Excluded from MA, only presented 32-36 week group	12 years (mean)	1996-1997	33-36 weeks: 57% 37-41 weeks: 52%	NR	General intellectual ability on Woodcock-Johnson III Tests of Cognitive Abilities	good
(van Baar et al., 2009)	The Netherlands	Excluded from MA, only presented 32-36 week group	8 years	1996 - 1999	Preterm 52% Term 47%	Dutch 91%	Revised Amsterdam Children's Intelligence Test (short version)	good
(Voigt et al., 2012)	Germany	Excluded from MA, only presented 32-36 week group	2 years (corrected)	2007-2008	32-37 weeks 51%, ≥38 weeks 47%	NR	Mental Scale of the Bayley Scales, 2nd edition	fair
(Yang, Platt and Kramer, 2010)	Belarus	37 weeks: 469 39–41 wks:11,074	6 years	1996-1997	38 weeks: 53.8% 39 weeks: 50.8% 40 weeks: 51.7%	NR	Wechsler Abbreviated Scales of Intelligence	good

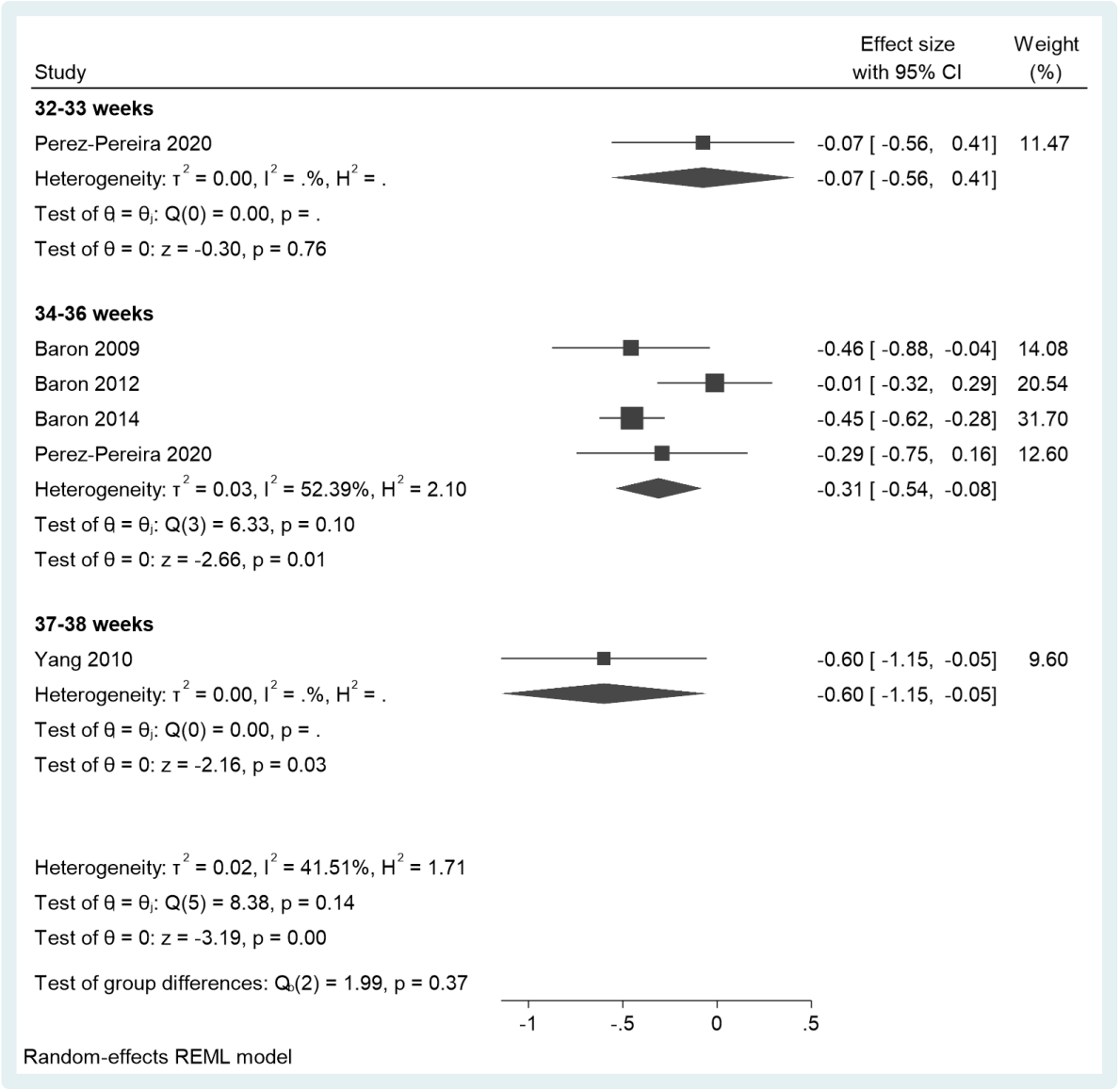


Figure 39 – Standardised mean difference in cognitive impairment scores by gestational age

Executive function problems

There was a total of 174 children from two studies (Brumbaugh (2014) and Hodel (2016)) included in this meta-analysis (Table 18). Both studies used The Behaviour Rating Inventory of Executive Function–Preschool Version (BRIEF-P) global executive composite score to assess executive function. The forest plot suggests there is no effect of prematurity on executive function, although note this is the smallest meta-analysis in the review (Figure 40).

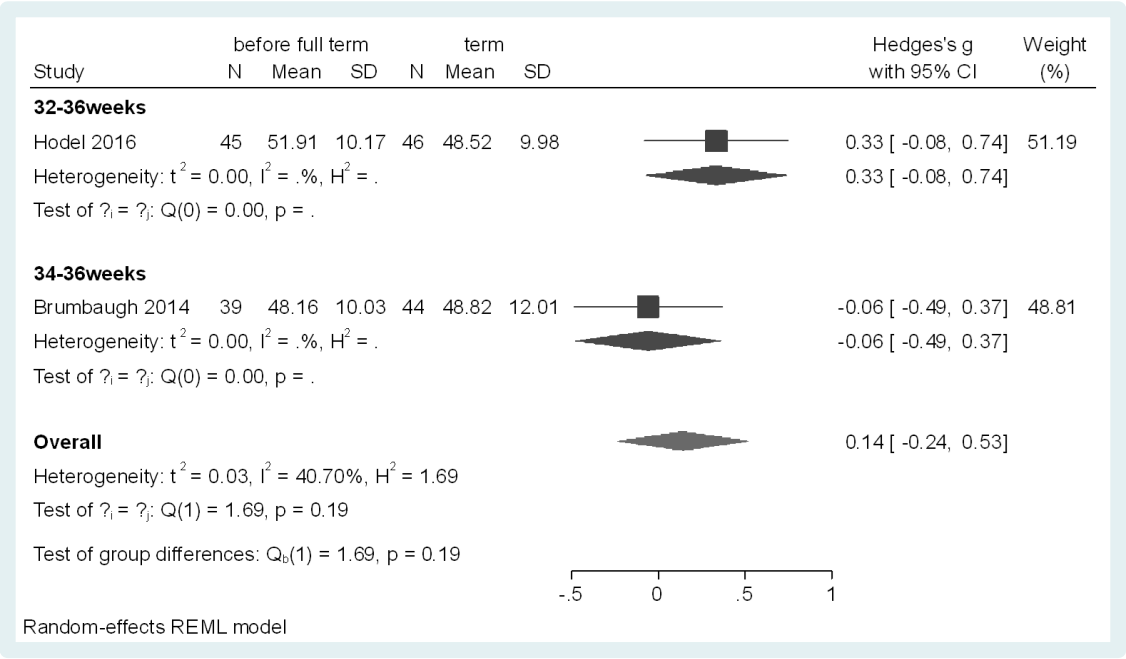


Figure 40 - Standardised mean difference in executive function scores by gestational age

Table 18 – Studies reporting executive function problems

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Study Quality
(Brumbaugh et al., 2014)	USA	32-34 weeks: 39 38-42 weeks: 44	4 years	2005 - 2006	32-34 weeks:59% 38-42 weeks: 50%	Not reported (NR)	The Behaviour Rating Inventory of Executive Function–Preschool Version (BRIEF-P)	fair
(Hodel et al., 2016)	USA	32–36 weeks: 45 37-42 weeks: 46	4.5 years	not stated	32–36 weeks: 51.1% 37-42 weeks: 54.3%	Caucasian 92%	The Behaviour Rating Inventory of Executive Function–Preschool Version (BRIEF-P)	fair

Educational outcomes – school readiness

Ten studies reported school readiness. There was a total of 283,659 children included in this meta-analysis, from seven studies, see Table 19. School readiness was measured by a mixture of routinely administered assessment collected via linked data, and specific tests carried out as part of cohort studies. The children were aged 3-5 years at the point of assessment. Quigley (2012) was excluded as it was superseded by a more recent study using the same cohort data (Poulsen (2013)). Bentley (2016) included the same children as Hanly (2018). Dhamrait (2021) was not presented because they only presented data for the 32-36 week group, and there was also a 32-33 week group and a 34-36 week group.

There appears to be an association between early educational outcomes and gestational age, but this is not statistically significant in the group of children born at 32-33 weeks (Figure 41) it is possible that this is because of relatively small sample sizes (only 199 children born 32-33 weeks).

The prevalence of non-school readiness is higher in the 37-38 week group compared to the term group and the 34-36 week group (Figure 42). This is largely a result of Morse (2009) which has a much lower prevalence in both the 34-36 week group and the term group compared to other studies but does not report results for 37-38 weeks.

Table 19 - Studies reporting non-school readiness by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (unless otherwise stated of whole cohort or of term group)	Tool / criteria for meta-analysis	Study Quality
(Bentley, 2016)	Australia	Excluded from MA- same cohort as Hanly (2018)	5 years	2002-2007	50.6%	"English as an additional language" 16.4%		good
(Crockett et al., 2022)	USA	34-36 weeks: 1,217 39-41 weeks: 15,203	Up to age 8	2000 - 2005	34-36 weeks: 53.6% 39–41 weeks: 51.1%	Not reported	Early developmental impairment – vulnerable in >1 domain	good
(Dhamrait, Christian, O'Donnell et al., 2021)	Australia	Excluded from MA, only presented 32-36 week group	4 - 5 years	2004	32-36 weeks 52.8% 37-38 weeks 50.8% 39-40 weeks 49.4%	Caucasian 82% Other 12.3% Indigenous Australian 5.7%	Developmentally Vulnerable on one or more domains of the Australian Early Development Census	good
(Hanly, Falster, Chambers et al., 2018)	Australia	34 - 36 weeks: 3,932 37-38 weeks: 20,951 39 -40 weeks: 43,199	5 years	2004-2007	whole cohort 50.7% (not reported by gestation)	Aboriginal 7%	Developmentally Vulnerable on one or more domains of the Australian Early Development Census	good
(Morse, Tang and Roth 2009)	USA	34-36 weeks: 7,152 ≥37 weeks: 152,661	4 years	1996-1997	34-36 weeks: 52.2% ≥37 weeks: 51.3%	Black: 21.32% White: 55.69% Other: 22.98%	An assessment 6 weeks into the school year by a kindergarten teacher by using a 16-item checklist indicating that the child does not yet have the skills needed to be a successful learner.	good
(Pettinger, Kelly, Sheldon et al., 2020)	UK	32–33 weeks: 65 34–36 weeks: 478 37–38 weeks: 2,355 39–41 weeks: 7,269	4 years	2007-2010	Whole cohort 52%	English as additional language: 45%	Good level of development on the Early Years Foundation Stage Profile.	good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (unless otherwise stated of whole cohort or of term group)	Tool / criteria for meta-analysis	Study Quality
(Poulsen et al., 2013)	UK	32–33 weeks: 134 34–36 weeks: 756 37–38 weeks: 2,558 39–41 weeks: 9,000	3 years	2000-2002	32-33 weeks: 59.7% 39–41 weeks: 50.6%	White British: 80-89%	Bracken School Readiness Assessment. Scoring under -1 SD below mean	good
(Quigley, Poulsen, Boyle et al., 2012a)	UK	Excluded from MA-same cohort as Poulsen 2013	4 years	2000-2002	34-36 weeks: 67% Whole cohort 51%	White British 86%; Mixed 4%; Pakistani/Bangladeshi 4%; Black or Black British 3%; Indian 2%; Other 1%		good
(Smithers, Searle, Chittleborough et al., 2015)	Australia	37-38 weeks: 3,374 39-40 weeks: 7,505	5 years (median)	2004	50%	Aboriginal and/or Torres Strait Islander 3.25%	Children scoring in the lowest 10% of the Australian Early Development Index categorised as developmentally vulnerable.	good
(Woythaler, McCormick, Mao et al., 2015)	USA	34-36 weeks: 950 ≥37 weeks: 4,900	5	2001	34-36 weeks: 53.6%, ≥37 weeks: 50.4%	White 81.1% Black: 14.6% Other: 4.3%	Total School Readiness - a composite measure derived from cognitive assessment battery conducted during the kindergarten year	good

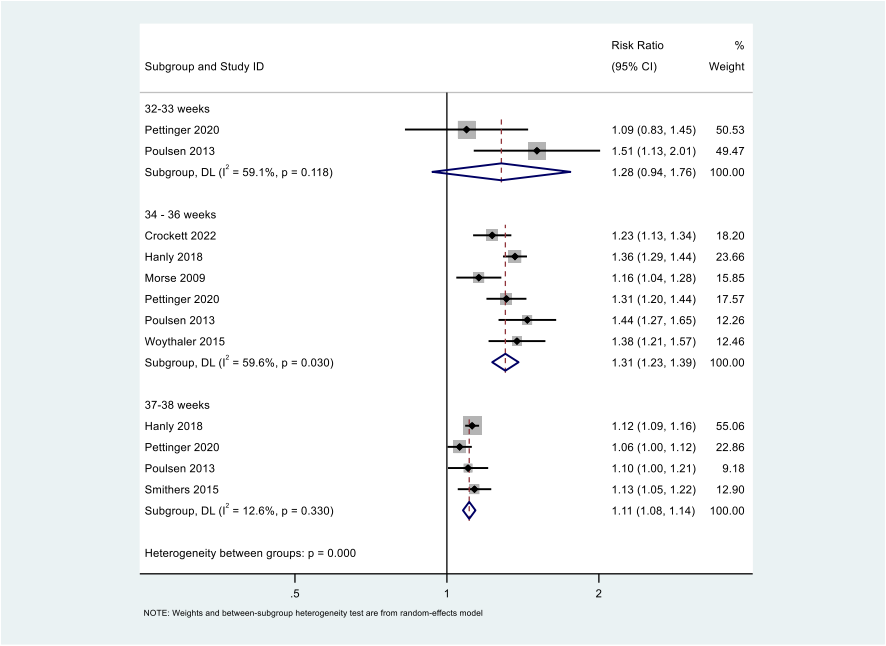


Figure 41 - Relative risk of non-school readiness by gestational age

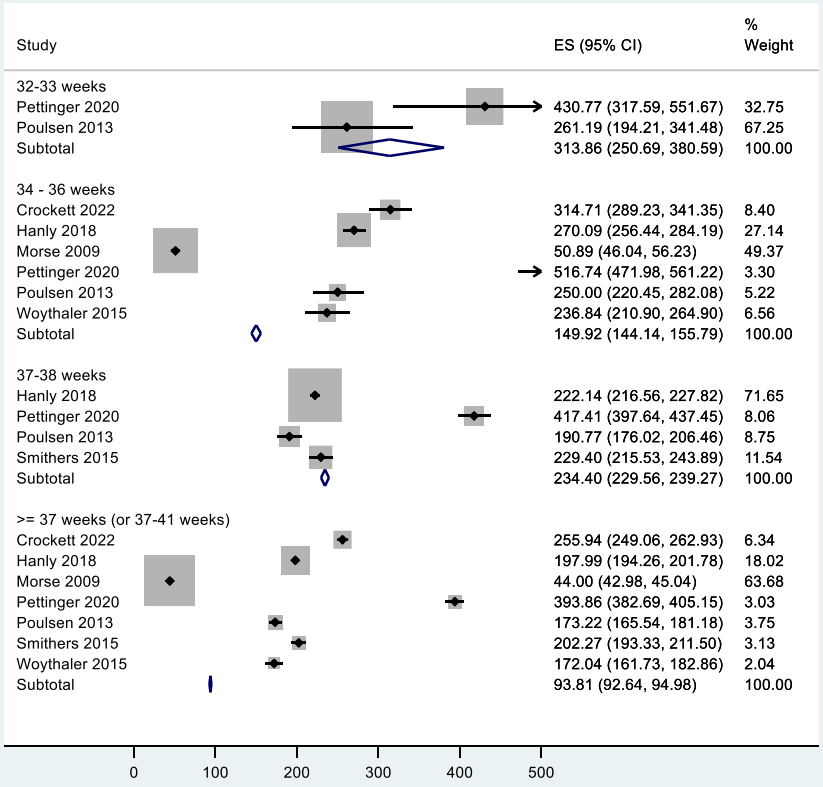


Figure 42 - Prevalence of non-school readiness by gestational age per 1,000 children

Educational Outcomes – age 6 – 11 years

There was a total of 576,150 children included in this meta-analysis across six studies, see Table 20. The children included were aged 6 – 9 years. Two studies were not included in the meta-analysis: Chan (2014), and Williams (2013). This is because there were more recent studies which used the same cohorts (Alterman (2022) and Richards (2015) respectively).

There is a clear increase in relative risk of educational difficulties aged 6-11 years in all gestational age categories compared to term born children, although the effect size is small, especially in the 37-38 week group (Figure 43).

The prevalence of low educational attainment is higher in the 37-38 week group compared to the 34-36 week group, but that is driven by one study – Richards (2015), which brings down the prevalence in the 34-36 week group but is not included within the 37-38 week group (Figure 44). Note the prevalence of low educational attainment in Crockett (2022) is much higher than other studies.

Table 20 - Studies reporting educational outcomes aged 6-11 years by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless more than 1% difference between gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Study Quality
(Alterman et al., 2022)	UK	32-33wks: 73 34-36wks: 430 37-38wks: 1,353 39-41wks: 4,724	11 years	2000-2001	32-33 weeks: 63.6% 34-36 weeks: 51.4% 37-38 weeks: 52.5% 39-41 weeks: 49.8%	White: 85.2%	Did not pass Mathematics Key Stage 2	good
(Brown, Quach, Anderson et al., 2019)	Australia	34 - 36 weeks: 76 37-38 weeks: 295 39 - 40 weeks: 471	8 - 9 years	2005-2006	52.0%	Not reported (NR)	Mathematics computation skill ≥1 SD below mean scores - Wide Range Achievement Test fourth edition	good
(Chan and Quigley, 2014)	UK	MCS data included via Alterman 2022	7 years	2000-2002	Whole cohort: 50% 34 - 36 weeks: 65%	White 86%	Not achieving ≥ expected in reading writing and maths in Key Stage 1 assessments	good
(Crockett et al., 2022)	USA	34-36 weeks: 1,339 39-41 weeks: 16,936	Up to age 8	2000 - 2005	34-36 weeks: 53.6% 39–41 weeks: 51.1%	NR	Grade 3 numeracy, linked data	good
(Libuy, Gilbert, Mc Grath-Lone et al., 2023)	UK	32-33 weeks: 2,142 34-36 weeks: 12,891 37-38 weeks: 55,585 39-40 weeks:149,923	11 years	2004-2005	32-33 weeks: 55.1% 34-36 weeks: 54.6% 37-38 weeks: 52.2% 39-40 weeks: 50.5%	White: 78.6%; Asian 10.1%; Black 5.0%; Any other ethnic group 1.4%; Mixed 4.9%	Not achieving expected level at Key Stage 2	good
(Richards et al., 2015)	USA	34 - 36 weeks: 25,850 37-41 weeks: 294,076	6-8 years	1998–2002	34 - 36 weeks: 52.9% 37-41 weeks: 50.4%	White non-Hispanic 55.6%; Black non-Hispanic 34.4%; Hispanic 10.0%	Academic performance - specifically mathematics failure on Criterion-Referenced Competency Tests	good
(Searle, Smithers, Chittleborough et al., 2017)	Australia	37-38 weeks: 3,762 40 weeks: 6,224	8 years	2000-2002	50.2%	NR	Below National Minimum Standard on National Assessment Program, numeracy	good

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless more than 1% difference between gestations)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Study Quality
(Williams, Dunlop, Kramer et al., 2013)	USA	Data included via Richards (2015)	6-7 years	1998 - 2003	50.6%	White 52.2% Black 37.0% Hispanic 10.8%		good

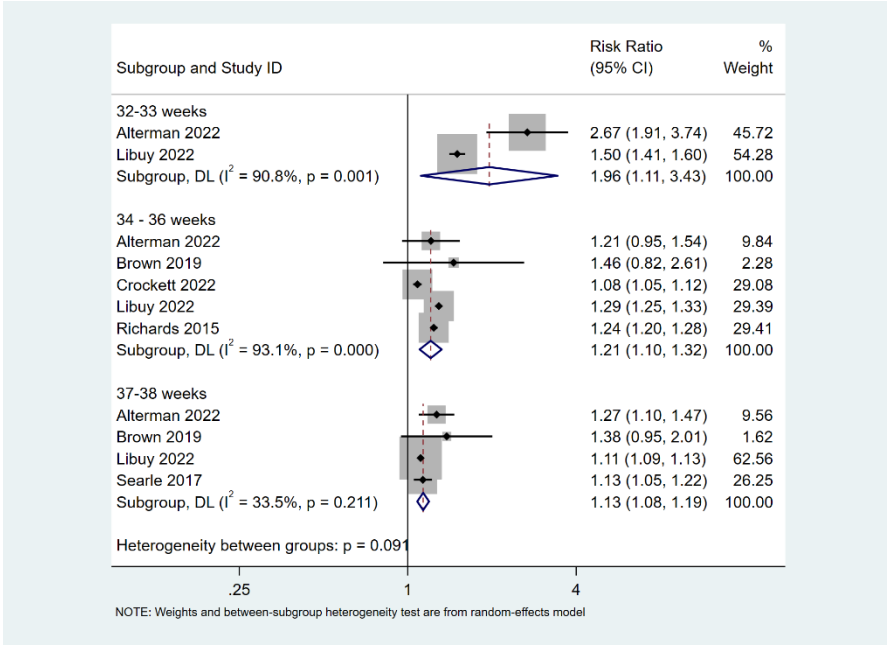


Figure 43 - Relative risk of low educational attainment aged 6-11 years, by gestational age

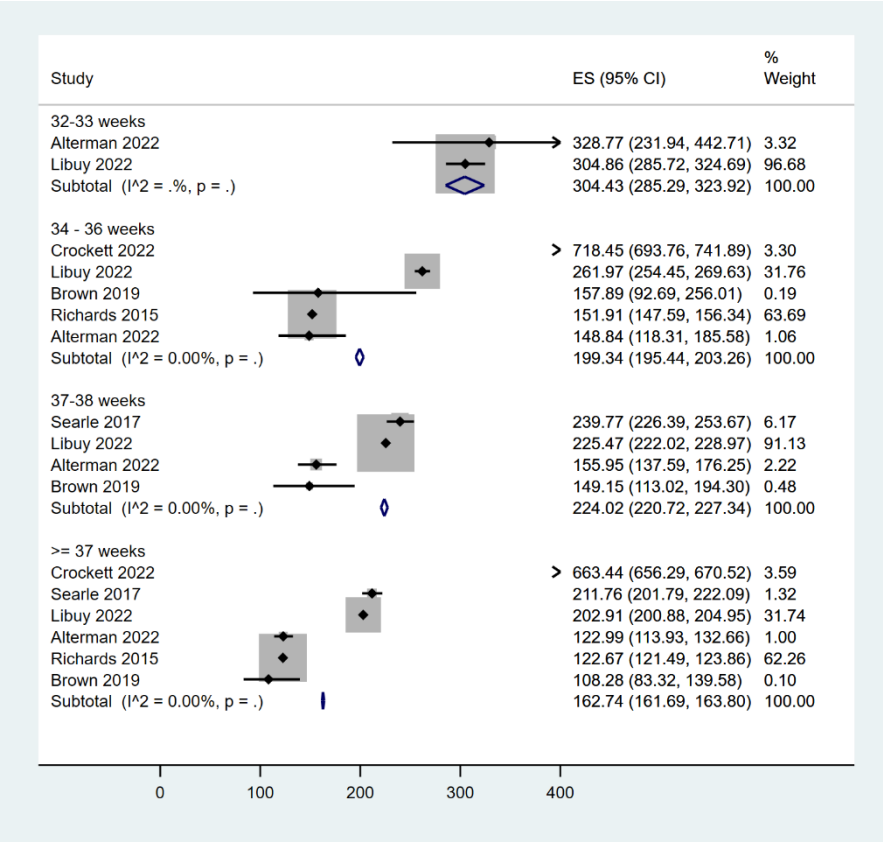


Figure 44 - Prevalence of low educational attainment aged 6-11 years by gestational age, per 1,000 children

Educational Outcomes – age 12 - 17 years

There were two studies which reported high school educational outcomes, they included 112,498 children in total (see Table 21). There was a trend towards increased risk of poor educational outcomes aged 12-17 amongst children born 32-38 weeks, but these fail to reach statistical significance, except in the early term group (Figure 45). Interpreting prevalence (Figure 46) is difficult because Berry (2018) and Alterman (2022) have quite different prevalences (likely due to different measurements of low attainment) and combining the groups 32-36 weeks was challenging because the authors divided the gestational categories differently.

Table 21 - Studies reporting educational outcomes aged 12-17 years by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless >1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or term group)	Tool / criteria for meta-analysis	Study Quality
(Alterman et al., 2022)	UK	32-33 weeks: 76 34-36 weeks: 401 37-38 weeks: 1,408 39-41 weeks: 4,896	16 years	2000-2001	32-33 weeks: 63.6% 34-36 weeks: 51.4% 37-38 weeks: 52.5% 39-41 weeks: 49.8%	White: 85.2%	Not achieving 5 General Certificates of Secondary Education (GCSE)	good
(Berry et al., 2018)	New Zealand	33-36 weeks: 8,343 (not meta-analysed) 37-38 wks: 27,540 39 - 40 wks: 78,177	15 or 16 years	1998 - 2000 and 2005 - 2015	51.4%	European 67%, Pacific Islander 12% Māori 21%	Unable to get National Certificate of Educational Achievement level 1 examination grade	good

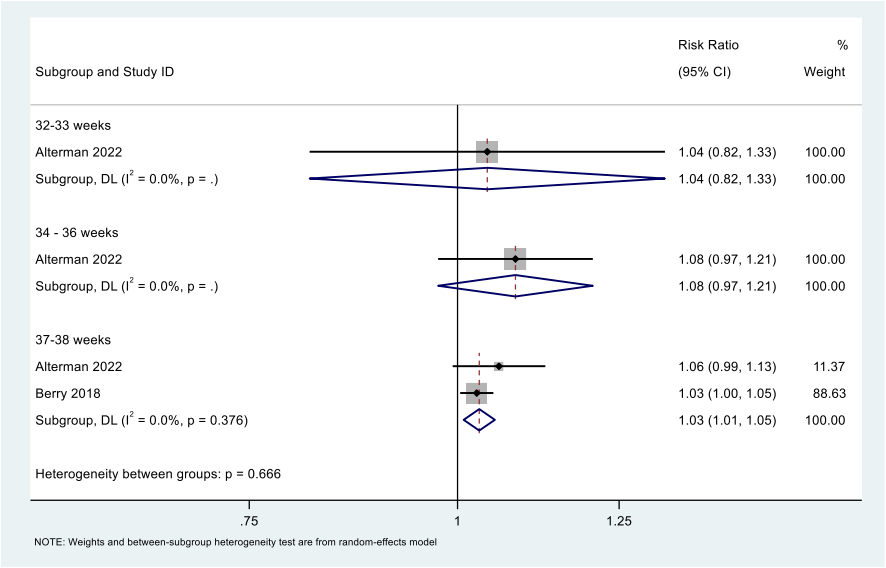


Figure 45 - Relative risk of low educational attainment aged 12-18 years by gestational age

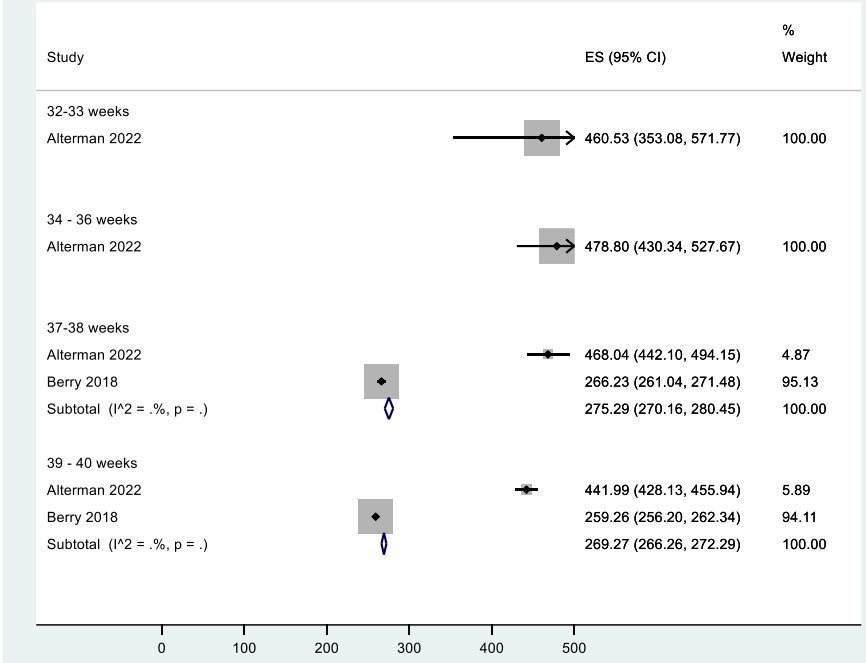


Figure 46 - Prevalence of low educational attainment aged 12-18, per 1,000 children

Educational Outcomes – continuous outcomes

Three studies were excluded from the meta-analysis because their data was already included in other educational outcome meta-analyses (Beauregard (2018a), Richards (2016) and Shah (2016b)). They all used ECLS-B, but that data was already included by Woythaler 2015. Beauregard (2018b) used Millennium Cohort Study (MCS) data which was already included by Poulsen (2013) in a binary format. The only remaining study reporting continuous outcomes was Wehby (2022); since there was only one study a meta-analysis has not been done. This used national percentile ranking scores for maths, science and reading, carried out when the children were 6 -16 years old. The authors found that the preterm children (32 – 36 weeks) performed significantly worse on all three domains compared to term children: maths -2.2 (-2.6, -1.83), reading -1.48 (-1.88, -1.07), science -1.02 (-1.36, -0.67).

Special Educational Needs and Disability (SEND)

There was a total of 1,244,844 children included in this meta-analysis across six studies (Table 22). The relative risk of SEND increases as gestational age decreases Figure 47. Prevalence is highest in the 32-33 week gestation group Figure 48. The only exception is in the 33-36 week group, but that is the result of a single study, which has consistently lower levels of SEND in each gestational group, but still shows the same trend in relative risk as the other studies.

Table 22 - Studies reporting special educational needs and disability (SEND) by gestational age

Record ID	Location	Total participants included in meta-analysis	Age at assessment	Birth year of participants	Gender: % male (whole cohort unless > 1% difference between gestational age groups)	Ethnicity of participants using same terminology as the studies (whole cohort or of term group)	Tool / criteria for meta-analysis	Study Quality
(Alterman et al., 2021)	UK	32-33 weeks: 135 34-36 weeks: 732 37-38 weeks: 2,460 39-40 weeks 6,051	11 years	2000-2002	Whole cohort: 51% 34-36 weeks: 64%	White 87.1%, Other 12.9%	Parents were asked whether the school or local education authority had ever told them their child has SEN	good
(Berry et al., 2018)	New Zealand	37-38 weeks: 69,363 39 – 40: weeks: 180,363	6 - 11 years	1998 - 2000 and 2005 - 2015	51.4%	European 67%, Pacific Islander 12% Māori 21%	Use of the Resource Teachers: Learning and Behaviour (RTLB) service	good
(Crockett et al., 2022)	USA	34-36 weeks: 2,088 39-41 weeks: 26,012	Up to age 8	2000 - 2005	34-36 weeks: 53.6% 39–41 weeks: 51.1%	Nor reported (NR)	Receipt of SEN funding	good
(Larsen et al., 2021)	Denmark	32-33 weeks: 6,067 34-36 weeks: 29,821 37-41 wks: 531,996	4-6 years	1997–2013	NR - only reported for each disorder not each gestation	NR	Linked data from the Danish special educational register	good
(Libuy et al., 2023)	UK	32-33 weeks: 2,227 34-36 weeks: 13,385 37-38 weeks: 57,955 39-40 wks: 156,376	11 years (key stage 2)	2004-2005	32-33 weeks: 55.1% 34-36 weeks: 54.6% 37-38 weeks: 52.2% 39-40 weeks: 50.5%	White: 78.6%; Asian 10.1%; Black 5.0% Any other ethnic group 1.4%; Mixed 4.9%	Ever had SEN provision in primary school (defined as those with a statement of SEN or an EHCP or Action, Action Plus or Support)	good
(Morse et al., 2009)	USA	34-36 weeks: 7,152 ≥37 weeks: 152,661	4 years	1996-1997	34-36 weeks: 52.2% ≥37 weeks: 51.3%	Black: 21.32% White: 55.69% Other: 22.98%	Exceptional student education on education records	good

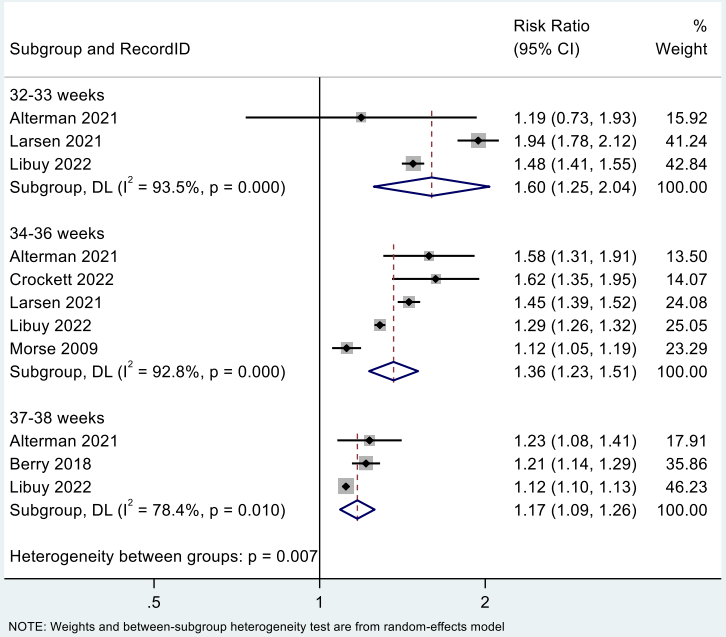


Figure 47 - Relative risk of Special Educational Need and Disability by gestational age

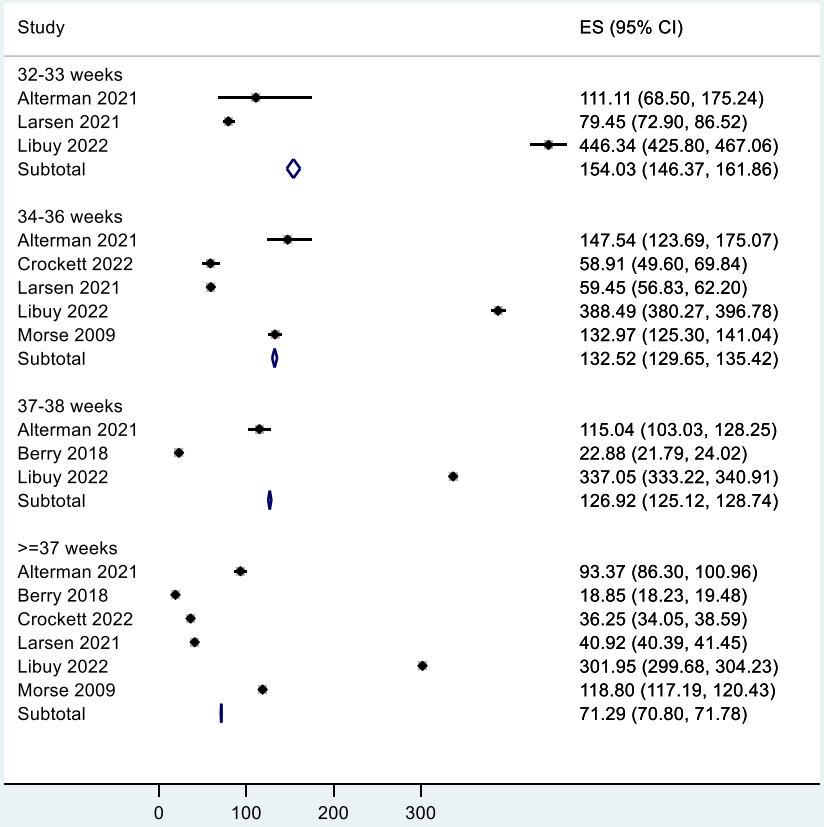


Figure 48 - Prevalence of Special Educational Need and Disability by gestational age, per 1,000 children

2.3.5. Sensitivity analyses

When only the papers with a full term (39-40/41 weeks) comparison group were included, only one paper remained in each gestational subgroup for CP and global developmental delay. The overall interpretation was unchanged in all cases (see Figure 49, Figure 50, Figure 51, Figure 52).

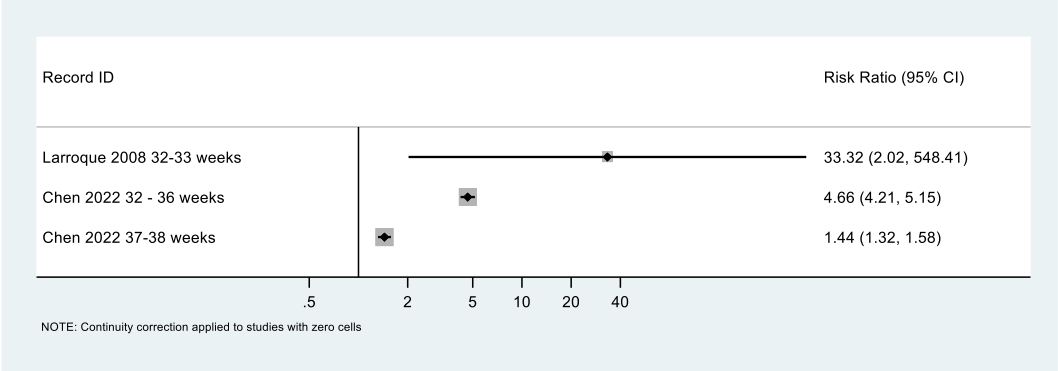


Figure 49 - Relative risk of CP by gestational age, only including studies with 'full' term comparison groups

Effect sizes are similar but larger, especially in the 32-33 week group, and the confidence intervals are wider. No studies remain in the 34-36 week group. The effect sizes are the same for the 37-38 week group, as this was previously based just on one study, which used a full term comparison group.

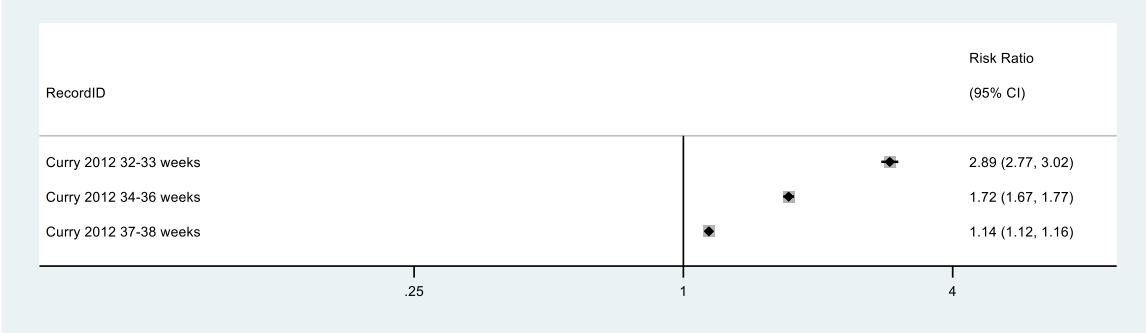


Figure 50 - Relative risk of global developmental delay by gestational age, only including studies with 'full' term comparison groups

Only one study used a full term comparison group. The 32-33 week group and the 37-38 week group are unchanged as previously were based only on one study. The effect size has increased slightly in the 34-36 week group, and the confidence intervals have narrowed.

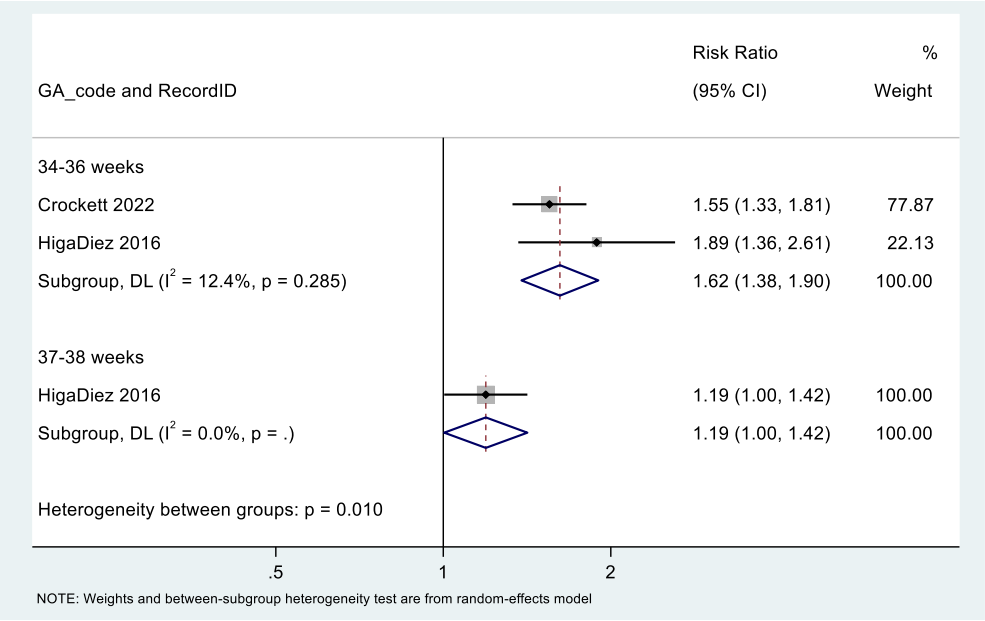


Figure 51 - Relative risk of ADHD by gestational age, only including studies with 'full' term comparison groups

All the studies investigating children born at 32-36 weeks used a ≥37 week term comparison group; the effect sizes in the other subgroups are unchanged.

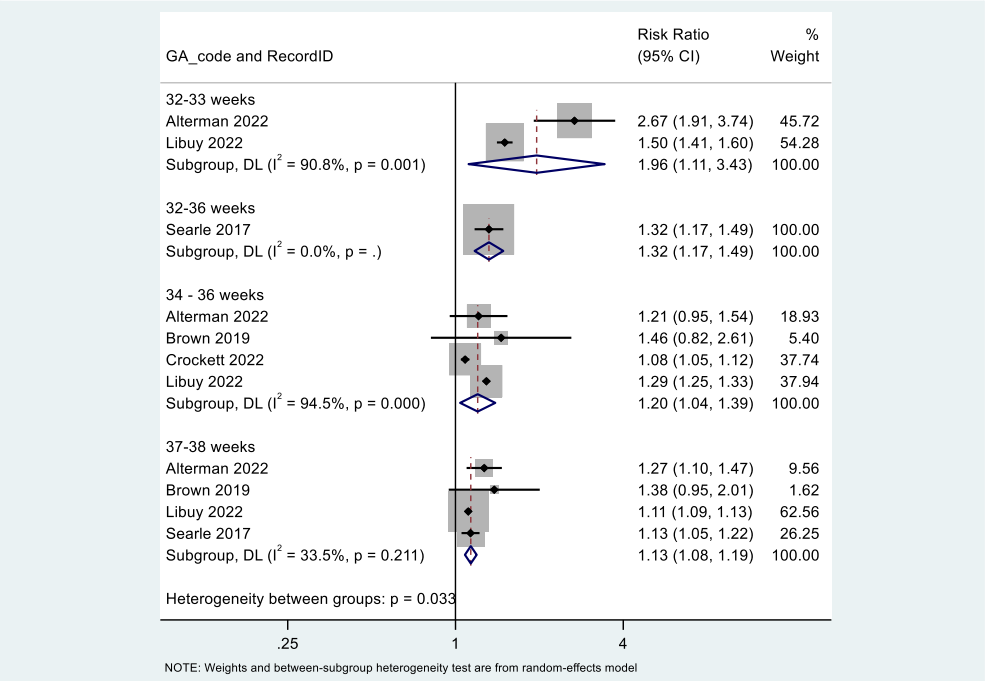


Figure 52 - Relative risk of low educational attainment by gestational age, only including studies with 'full' term comparison groups

The only estimate that has changed is for the 34 – 36 week group, where Richards (2015) has been removed, which has slightly reduced the relative risk and widened the confidence intervals.

2.3.6. Publication bias

Egger's tests and funnel plots are summarised in Table 23. Non-significant p-values >0.05 indicate low risk of publication bias (Egger, Davey Smith, Schneider et al., 1997).There are also other causes for asymmetrical funnel plots related to study design, such as lack of blinding, which was the case in many studies included in this review (Sedgwick and Marston, 2015). Funnel plots are shown in appendix 2.4. In general, the symmetrical funnel plots corresponded with a non-significant Egger's test, although there were a few exceptions, as shown below there was evidence of publication bias for motor delay, language delay, cognitive impairment, and ASD meta-analyses.

Table 23 - Funnel plots and Egger's tests summary

Meta-analysis	**Number of studies in meta-analysis**	**Visual inspection of funnel plot**	**P value of Egger's test**
Cerebral palsy	8	Symmetrical	0.95
Developmental coordination disorder	2	Symmetrical	1.00
Visual impairment	5	Symmetrical	0.10
Hearing Impairment	3	Symmetrical	0.88
Sleep apnoea	1	N/A	N/A
Autism spectrum disorder	3	Asymmetrical	0.02
SEB – global (binary)	2	Symmetrical	0.41
SEB – global (continuous)	2	Asymmetrical	0.01
SEB – internalising behaviours	3	Symmetrical	0.95
SEB – externalising behaviours	1	N/A	N/A
SEB – social	2	Asymmetrical	0.03
ADHD (binary)	5	Symmetrical	0.67
ADHD symptoms (continuous)	7	Symmetrical	0.81
Global developmental delay	3	Symmetrical	0.13
Motor delay	7	Asymmetrical	<0.01
Language delay	6	Asymmetrical	0.01
Cognitive delay	5	Symmetrical	0.55
Cognitive impairment (binary)	6	Asymmetrical	0.05
Cognitive impairment (continuous)	5	Symmetrical	0.05
Executive function (continuous)	2	Symmetrical	Convergence not achieved
Education –school readiness	7	Symmetrical	0.35
Low educational attainment aged 6 – 11 years	6	Symmetrical	0.16
Low educational attainment aged 12 – 17 years	2	Symmetrical	Convergence not achieved
Special Educational Needs and Disabilities	6	Asymmetrical	0.22

SEB: social, emotional, behavioural. ADHD: attention deficit hyperactivity disorder.

2.3.7. Prevalence summary

The following bar charts were produced to facilitate easy comparison of the prevalence of different developmental disorders.

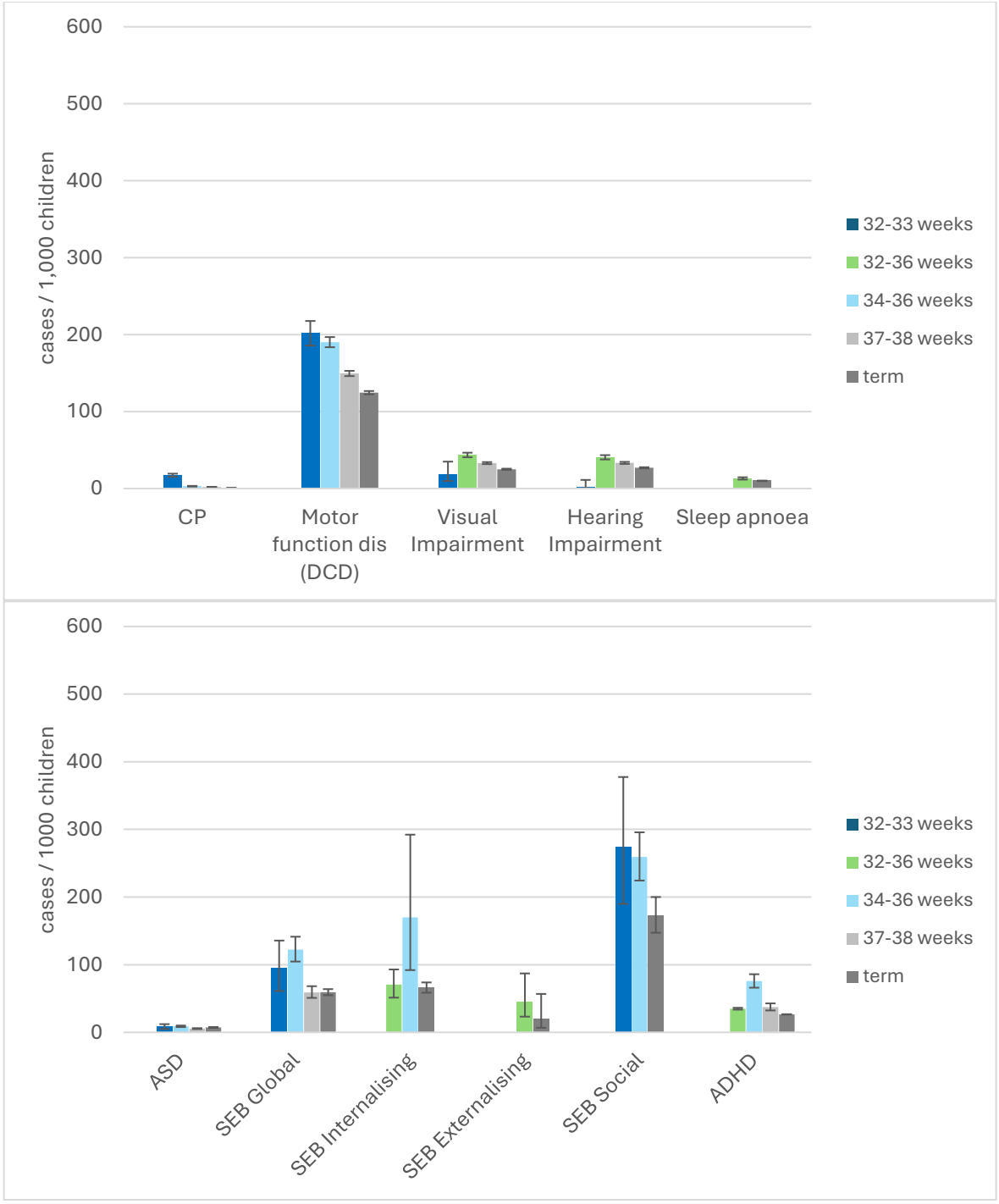


Figure 53 - Prevalence of developmental disorder by gestational age per 1,000 children (1)

CP: cerebral palsy, DCD: developmental co-ordination disorder, ASD: autism spectrum disorder, SEB: social/emotional/behavioural problems, ADHD: attention deficit hyperactivity disorder.

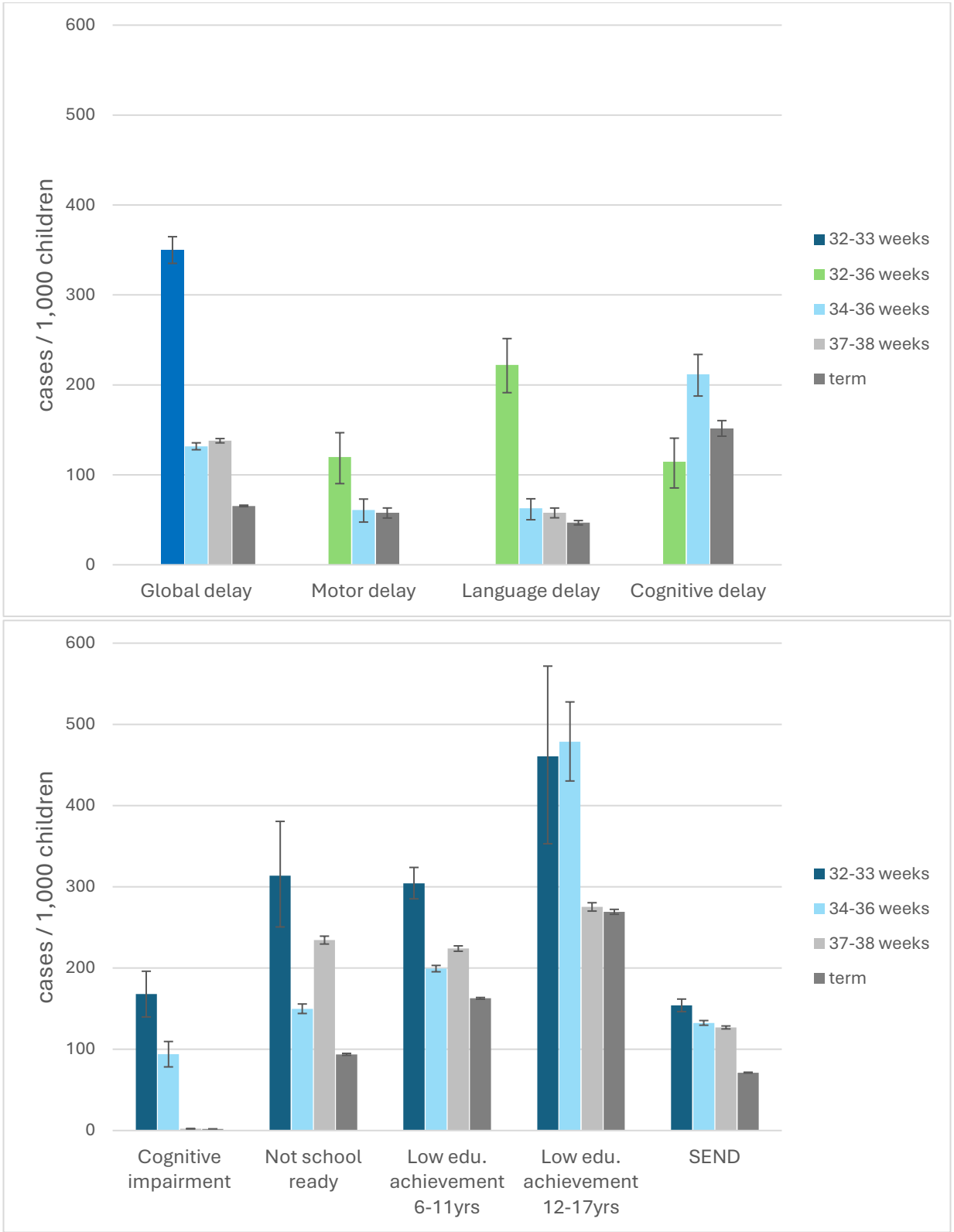


Figure 54 - Prevalence of developmental disorder by gestational age per 1,000 children (2)

SEND: Special educational needs and disabilities

2.3.8. Summary table

The findings from the meta-analyses are summarised in Table 24.

Table 24 - Summary of relative risk and prevalence of developmental disorders

↑: increased RR with CI not crossing "1", or increased prevalence compared to term, with CI not overlapping with term. ↓: reduced RR with CI not crossing "1", or decreased prevalence compared to term, with CI not overlapping with term.
↔: difference not statistically significant. dark grey = no data. Light grey = not presented (data available for both 32-33 week and 34-36 week groups)

Developmental disorder	32-33 weeks	32-36 weeks	34-36 weeks	37-38 weeks
CP relative risk	↑		↑	↑
CP prevalence	↑		↑	↑
DCD relative risk	↔		↑	↑
DCD prevalence	↑		↑	↑
Visual impairment relative risk	↔	↔		↑
Visual impairment prevalence	↔	↑		↑
Hearing impairment relative risk	↔	↔		↑
Hearing impairment prevalence	↓	↑		↑
Sleep apnoea relative risk		↑		
Sleep apnoea prevalence		↑		
SEB global relative risk	↔		↑	↔
SEB global prevalence	↔		↑	↔
SEB global (continuous)		↓	↔	
SEB internalising relative risk		↔	↔	
SEB internalising prevalence		↔	↑	
SEB externalising relative risk		↔		
SEB externalising prevalence		↔		
SEB social relative risk	↑		↑	
SEB social prevalence	↔		↑	
ADHD relative risk		↑	↑	↑

Developmental disorder	**32-33 weeks**	**32-36 weeks**	**34-36 weeks**	**37-38 weeks**
ADHD prevalence		↑	↑	↑
ADHD (continuous)		↔	↑	↔
ASD relative risk	↑		↑	↔
ASD prevalence	↔		↑	↓
Global developmental delay relative risk	↑		↑	↑
Global developmental delay prevalence	↑		↑	↑
Language developmental delay relative risk		↔	↑	↔
Language developmental delay prevalence		↑	↑	↑
Motor developmental delay relative risk		↔	↔	
Motor developmental delay prevalence		↑	↔	
Cognitive developmental delay relative risk		↑	↑	
Cognitive developmental delay prevalence		↔	↑	
Cognitive impairment relative risk	↑		↔	↑
Cognitive impairment prevalence	↑		↑	↑
Cognitive impairment (continuous)	↔		↑	↑
Executive function (continuous)		↔	↔	
Not school ready relative risk	↔		↑	↑
Not school ready prevalence	↑		↑	↑
Low educational attainment 6 -11 years relative risk	↑		↑	↑
Low educational attainment 6 - 11 years prevalence	↑		↑	↑
Low educational attainment 12-17 years relative risk	↔		↔	↑
Low educational attainment 12-17 years prevalence	↑		↑	↔
Special educational needs and disabilities relative risk	↑		↑	↑
Special educational needs and disabilities prevalence	↑		↑	↑

2.4. Discussion

2.4.1. Key findings

This chapter described the research conducted to fulfil the first objective of this thesis:

1. To conduct a systematic review and meta-analyses to determine the risk and prevalence of developmental disorders amongst children born between 32-38 weeks compared to children born at term.

The key findings were:

- Children born between 32-38 weeks are at increased risk of developmental disorders compared to children born at "term" (which was defined in a variety of ways by the studies and was usually not "full term" as defined the Chapter 1 – Background). In most cases an inverse gradient association with gestational age was demonstrated.
- There was a statistically significant increased relative risk and prevalence of developmental disorder amongst all gestational age groups born 32 – 38 weeks for the following conditions: cerebral palsy, sleep apnoea, ADHD, global developmental delay, low educational attainment aged 6-11 years, and SEND.
- Whilst the highest increased relative risk compared to children born at term was for children born 32-33 weeks for cerebral palsy, cerebral palsy has a low prevalence compared to other developmental disorders.
- The most prevalent developmental disorder amongst the children born 32-38 weeks was low educational attainment, across all age ranges.
- The meta-analyses showed that children born early term, compared to full term children, are at increased risk and have a higher prevalence of: ADHD, global developmental delay, language delay, motor delay, cognitive delay, cognitive impairment, non-school readiness, low educational attainment aged 6 -11 years, and SEND.

There is a clear increase in both the relative risk and prevalence of ADHD in children born 32-38 weeks compared to children born full term. There appears to be some association with reduced gestational age and increased risk of some forms of social, emotional and behavioural problems. The most prevalent problem of this type is social problems, such as the ability to show empathy or play with other children (Cheong et al., 2017)). The 32-36 week group (but not the 32-33 and 34-36 week groups) had overlapping confidence intervals with the prevalence of social problems with the full term group, but this is likely the result of the mechanics of the meta-analysis, and which studies were included in which gestational age bracket. There was a very small increased risk and prevalence of ASD, but only seen in the 34-36 week group, and surprisingly the prevalence of ASD was much lower than ADHD. In terms of developmental delay, the association between increased risk and prevalence of a global delay or a language delay seems clear and is evident in all gestational age groups 32-38 weeks. The effect was only seen in the 32-33 week group for motor delay. The cognitive developmental delay meta-analysis is hard to interpret; the prevalence of cognitive delay is relatively high in the full term group, and the confidence intervals overlap with the 32-36 week group. However, in the relative risk meta-analysis, we see a clear increased risk of cognitive delay in the 32-36 week group, in fact this is one of the highest increased relative risks in across the review (3.6, 95% confidence intervals 2.1 - 6.0). Again, it is likely that the picture seen in the prevalence is a result of which studies reported different gestational ages.

There were several disorders where there was no data for early term children. When subgroup analysis was possible, this sometimes contained data from only one study. However, since early term birth is relatively common, when this group was included, even if the participants were only from one study, it often represented a large number of children. The meta-analyses have shown early term children are at increased risk and have a higher prevalence of: ADHD; global developmental delay; language delay; motor delay; cognitive delay; cognitive impairment; non-school readiness; low educational attainment at 6 -11 years and SEND.

There were two conditions (hearing impairment, ASD) where one group born before full term has a lower prevalence of developmental disorder than the full term group. In each case there was only one study in that gestational age group (Larroque 2008 in the hearing MA, Leavey 2013 in the ASD meta-analysis) that was contributing to this effect, and it is most likely a result of different measurements of for the disorders, as opposed to a protective effect of birth before full term in these conditions. The prevalence of cognitive delay is relatively high in the full term group, and the confidence intervals overlap with the 32-36 week group. However, in the relative risk

meta-analysis, we see a clear increased risk of cognitive delay in the 32-36 week group, in fact this is one of the highest increased relative risks in across the review (3.6, 95% confidence intervals 2.1 - 6.0). Again, it is likely that the picture seen in the prevalence is a result of which studies reported different gestational ages.

The only conditions which were found to have neither an increased relative risk nor prevalence amongst children born between 32-36 weeks was externalising behaviours, but this was based on only one study. There was no increased relative risk of executive function disorders and there is no prevalence calculation for this since it was reported as a continuous outcome. There was no evidence available regarding feeding problems.

These findings are largely consistent with previous research which has shown increased risk of developmental disorders amongst children born moderately preterm, late preterm, and early term (Nielsen et al., 2019; Allotey, Zamora, Cheong-See et al., 2018; Chan et al., 2016; Johnson et al., 2015a). This review demonstrates that difficulties faced by children born 32-38 weeks persist through childhood, with evidence of increased risk and prevalence of cognitive impairment and low educational attainment aged 6-11 years, in contrast to previous research suggesting developmental delay in preterm infants may be transient (Patel, 2016; Schmidt, 2012).

2.4.2. Strengths and limitations

This was a comprehensive review. There was a total of over 8 million children included in the meta-analyses. Calculating prevalence of a full range of developmental disorders meant the increased relative risk associated with gestational age could be contextualised and prevalence of different developmental disorders across gestational ages could be compared.

However, whilst there were a large number of children in total, because each developmental disorder was considered separately according to gestational age subgroups, there were sometimes small numbers in each subgroup.

The majority of studies were from more economically developed countries, and all were published in English, which could limit generalisability.

Including children <32 weeks gestation would have made this review unmanageably large but meant the prevalence and relative risk for the children born at 32-38 weeks could not be directly compared to very preterm children.

The children in the studies were assessed at different ages making meaningful combination of studies' results more difficult, since different conditions are more common at different ages.

The methods for determining gestational age were sometimes unclear and varied between studies. This may have an impact on the certainty of findings or could introduce a source of bias. Term comparator groups were very variable, for example ≥ 37 weeks, >37 weeks, ≥39 weeks, 39-41 weeks, or 40 weeks. This could account to some extent for why the prevalence of some conditions (e.g., poor school readiness ≤5 years and low educational attainment 6-11 years) is lower in the 37-38 week group than in the term group. Whilst it would have been preferable to have a homogenous term comparator group, only including studies which used a *full* term (39-40/41 weeks) comparison group would have resulted in a substantial loss of data; of the studies which were meta-analysed, only 24 used a full term comparison group. A sensitivity analysis was undertaken for CP, global developmental delay, educational outcomes aged 6 -11 years and ADHD, where only the papers with a full term comparison group were included and the overall interpretation was unchanged. Some of the included studies used atypical term comparator groups. For example, Polic (2017) and Klassen (2004) only included children who had been admitted to the neonatal unit, meaning that the full term group will be very different that a typical term control group; if a term born baby needs to be admitted to the neonatal unit it is likely that they are significantly unwell, as opposed to it being routine practice due to prematurity or for observation.

The biggest challenge with was the variety of tools used to measuring outcomes. This was partly addressed by carrying out multiple different meta-analyses to try to ensure that the combinations were reasonable. However, it is still important to acknowledge that whilst some studies used diagnostic codes in medical records to determine their outcome, many studies used questionnaires, tests, and tools (e.g., the Ages and Stages Questionnaire) which were not developed to make formal diagnoses, but rather were intended as screening tools for developmental problems (Zhou et al., 2020). Although some children may screen positive for a potential developmental disorder or be highlighted as a “cause for concern”, that does not equate to a formal diagnosis of a specific developmental disorder.

2.4.3. Implications for thesis

Whilst the findings of the systematic review suggest that children born 32-38 weeks gestation are at increased risk of developmental disorders, these were all unadjusted analyses (even where effect sizes were imported directly), and so it is unknown whether the effects would persist after adjusting for covariates.

Aside from the key findings of the systematic review listed above, the systematic review also found that the majority of UK research exploring developmental outcomes of children born before full term used educational attainment or SEND as the outcome measure and it is unclear to what extent developmental disorders and educational outcomes intersect (Alterman et al., 2022; Libuy et al., 2023; Alterman et al., 2021; Pettinger et al., 2020; Odd et al., 2019; Chan and Quigley, 2014; Odd et al., 2012; Quigley et al., 2012a; Mackay et al., 2010).

In all these cohorts >70% of the participants were White. Indeed, globally most data relating to developmental outcomes of children born preterm relates to White children (Pettinger et al., 2023). Therefore, the relationship between prematurity and developmental disorders amongst ethnic minorities in the UK is unknown.

The review has confirmed that early term born children are at increased risk of many developmental disorders, and therefore for the remainder of the thesis the early term children will be analysed separately from the other term born children, i.e. there will be a 37-38 week group and a 39-41 week full term group.

2.4.4. Chapter summary

This chapter has described a systematic review and meta-analysis to determine the risk of developmental disorder amongst children born between 32-38 weeks. Relative risk and prevalence of each developmental disorder have been calculated. This review has found evidence of an inverse relationship between gestational age and the majority of developmental disorders although this did not always reach statistical significance. Low educational attainment, DCD, global developmental delay, and cognitive impairment were the most prevalent disorders amongst children born 32-38 weeks. Some of the increased risks are small but may have a large impact both clinically and economically at a population level, as birth between 32-38 weeks is common. For many gestational subgroups the available evidence regarding developmental disorders is scant and gaps in the empirical knowledge persist. The majority of evidence was from outside of the UK, and there was very sparse evidence pertaining to children from minoritised ethnic backgrounds within the UK.

The next chapter describes the methods for the secondary data analysis using Born in Bradford data to explore the incidence of developmental disorders and the associated risk factors amongst children born before full term, amongst a majority Asian heritage cohort.

Chapter 3: Secondary Data Analysis Methods: The Born in Bradford Study

3.1. Introduction

Chapter 2 described a systematic review and meta-analysis conducted to determine the risk and prevalence of developmental disorders amongst children born between 32-38 weeks compared to children born at term. The review found that children born moderately preterm are at increased risk of being diagnosed with (or screening positive for) most developmental disorders compared with term born children. This association was also demonstrated in late preterm and early term groups, but effect sizes were smaller. There was a paucity of evidence regarding developmental disorders in children born before full term from minoritised ethnic groups in the UK. Due to the high number of participants from a South Asian background, the Born in Bradford cohort (BiB) is a useful dataset to investigate this evidence gap. The following chapters describe research using BiB data with linked health and educational data designed and undertaken to address the second - seventh objectives described in Chapter 1: Background:

2. To develop a list of clinical codes for primary and secondary care which correspond to the signs, symptoms, and diagnosis of the developmental disorders listed in the NICE guideline for developmental follow-up of children and young people born preterm (NICE, 2017b)
3. To determine the cumulative incidence and incidence rates of any developmental disorder, and of individual developmental disorders, in the Born in Bradford cohort
4. To explore how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity
5. To investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models
6. To carry out a latent class analysis to identify profiles of developmental outcomes
7. To determine which factors are associated with different profiles of developmental disorders

The remainder of this chapter describes the methods used to meet these objectives. This begins with an introduction to the data source: the Born in Bradford (BiB) cohort study. Following this, the exposure variable (gestational age), outcome variables (developmental disorders and SEND), and covariates are described. The development of the analysis cohort and sub cohort are described next. Finally, the statistical methods are described and detailed.

3.2. The Born in Bradford study

The Born in Bradford cohort study was set up to investigate high rates of infant and childhood morbidity and mortality in Bradford (McEachan, Santorelli, Watmuff et al., 2024; Wright, Small, Raynor et al., 2013). Bradford is the 6th largest city in the UK and many of its inhabitants live in poverty: approximately 70% of residents live in the most deprived fifth of the national population, according to the 2010 Index of Multiple Deprivation (Wright et al., 2013). Approximately 20% of the population is South Asian, 90% of whom have Pakistani heritage (Wright et al., 2013).

Bradford is served by a single maternity unit, based at the Bradford Royal Infirmary, part of Bradford Teaching Hospitals NHS Trust. Overall, 12,453 women were recruited to the cohort during their pregnancies, between March 2007 and November 2010. The majority of participants were recruited during the oral glucose tolerance test for gestational diabetes, which is carried out at 26-28 weeks gestation as part of routine antenatal care in Bradford. This meant there are very few extremely preterm babies in the cohort, although some mothers were recruited after the baby's delivery, at other hospital appointments or whilst postnatal inpatients. To maximise recruitment, baseline interviews were carried out in a range of languages commonly spoken in Bradford (in addition to English), specifically Mirpuri, Urdu, Bengali, and Punjabi. As well as a lower proportion of preterm babies in the BiB cohort deliveries (5.8% in the BiB cohort vs., 8.9% non-BiB cohort), there were some other differences between the recruited cohort and non-cohort births as follows: lower proportion of mothers aged 20 - 24 years (7.2% in BiB, 8.2% not in BiB); higher proportion of South Asian mothers (50.1% in BiB, 46.6% not in BiB); lower proportion of babies delivered vaginally (77.6% in BiB, 82.7% not in BiB); lower proportion of preterm (<37 week) deliveries (5.8% in BiB, 8.9% not in BiB) (Wright et al., 2013). This is only partly explained by the recruitment at 26-28 weeks since extremely preterm babies make up a very small minority of preterm births, most preterm deliveries are late preterm (see Table 1 - Birth characteristics by gestational age in England and Wales: 2021).

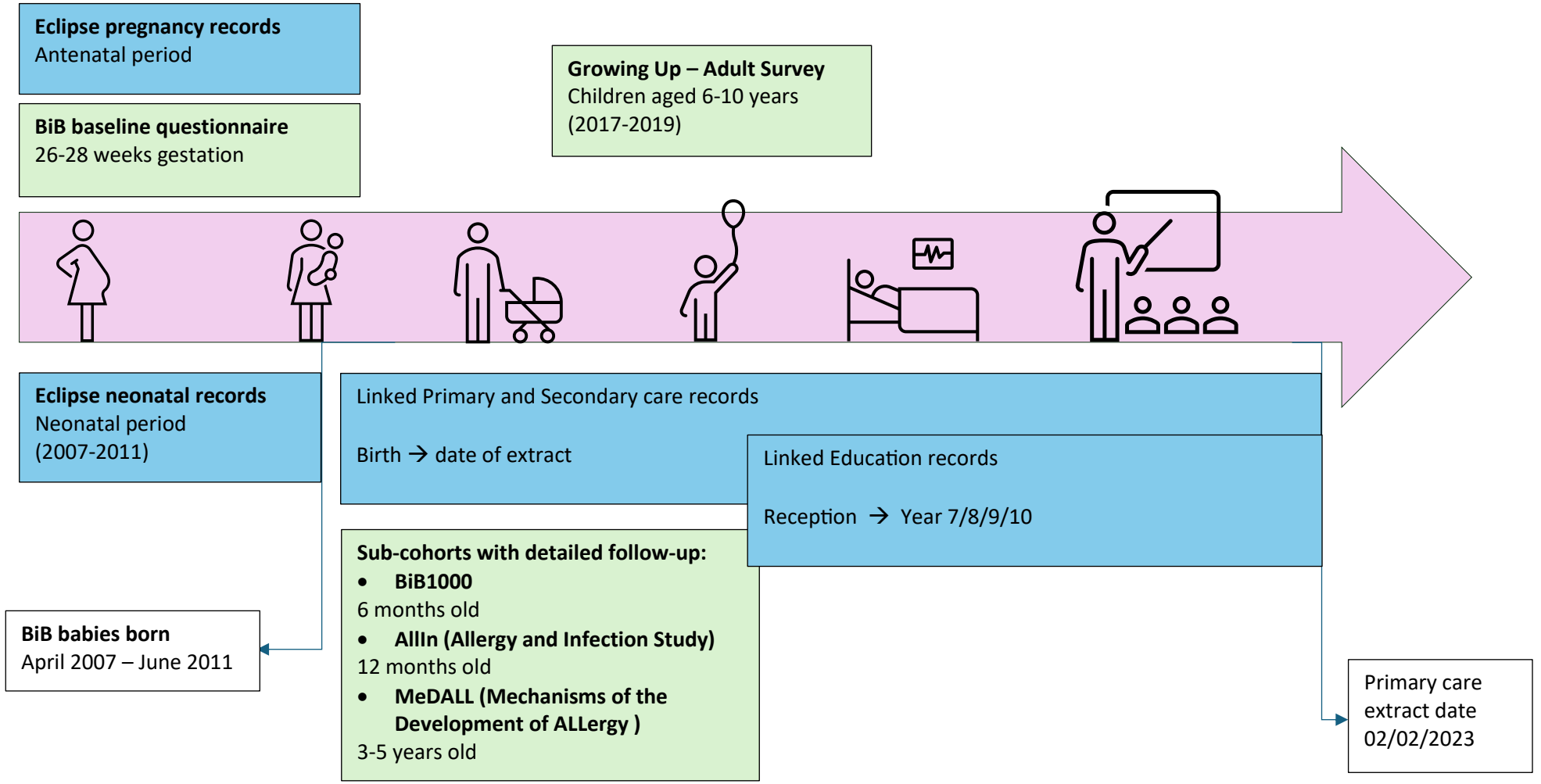
Data collection consisted of a series of questionnaires for parents and more recently for children, collected at specific time points or ages (Figure 55). The Born in Bradford data team also receive education data annually for participating children, if they are in state funded education.

Ethical approval

Ethical approval was covered by the approval for the original cohort study: Bradford Research Ethics Committee (Ref 07/H1302/112).

Figure 55 – The Born in Bradford (BiB) data sources planned to be used for analyses

Blue boxes are routinely collected linked data; green boxes are data collected specifically for BiB, by their research team. The boxes above the pink arrow are parent data, and the boxes below are child data. Eclipse = electronic maternity information system



3.3. Data access and management

The BiB executive committee approved access to the cohort and linked medical and education records data on 11th January 2021. An amendment was submitted in August 2023 to obtain the following data:

- Consanguinity
- Breastfeeding data from AllIn (Allergy and Infection Study), MeDALL (Mechanisms of the Development of ALLergy) and BiB1000
- Children's secondary care data

The amendment was approved by the executive committee on 9th August 2023.

The University of York "Code of practice and principles for good ethical governance", as well as the "University of York Data Protection Policy" and the "University of York Special Categories of Personal Data Policy" were followed. Data were stored on University of York servers, accessed via password, and automatically backed up. As per the data sharing agreement with Born in Bradford no data or any part of them came into the possession or control of any other organisation or any individual other than employees of University of York involved and named in the study. The data were not stored on any personal devices. Only data necessary for the aims and objectives of the work were shared from the Born in Bradford team. Personally identifiable data were not requested, given access to, or shared by the BiB team. The data were pseudonymised and provided from the Born in Bradford study via secure connection (Kiteworks) in accordance with their policies.

Quality assurance

Quality assurance for Born in Bradford data is described as follows: "All data collection is administered or undertaken by trained staff using standard operating procedures. Staff collecting data receive training in information governance and safeguarding as well as the assessments/data collection they are responsible for. We have regular training updates and observation of data collection with feedback as appropriate."(Bird 2019) Available here:

https://link.springer.com/article/10.1186/s12889-019-7222-2

The data for the platform study were collected as follows, which included multiple quality control mechanisms:

https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-8-327

https://academic.oup.com/ije/article/42/4/978/655870?login=false

3.4. Variables

3.4.1 The exposure variable

The exposure variable was gestational age, measured in weeks, to the last completed week. Gestational age is 'rounded down' by convention, therefore a baby born at 33 weeks and 6 days would be "33 weeks gestation". As per Figure 55 this data was collected via the mothers' Eclipse pregnancy records.

3.4.2.1. The outcome measure – medical records

All the conditions listed in the guidelines from the National Institute for Health and Care Excellence (NICE) for developmental follow-up of children and young people born preterm (NICE, 2017b) were considered, that is:

1. Cerebral palsy
2. Motor function problems, including developmental coordination disorder (previously known as dyspraxia)
3. Learning disability (intellectual disability)
4. Special educational needs and disabilities (SEND) and low educational attainment, here after referred to as "Education problems" to avoid confusion with SEND from education records
5. Executive function problems
6. Speech, language, and communication problems
7. Hyperactivity, impulsivity, and inattention, including Attention Deficit Hyperactivity Disorder (ADHD)
8. Autism spectrum disorder (ASD)
9. Emotional and behavioural problems
10. Feeding problems
11. Visual impairment
12. Hearing impairment
13. Sleep apnoea
14. Developmental delay

This section therefore corresponds to the second objective of the thesis;

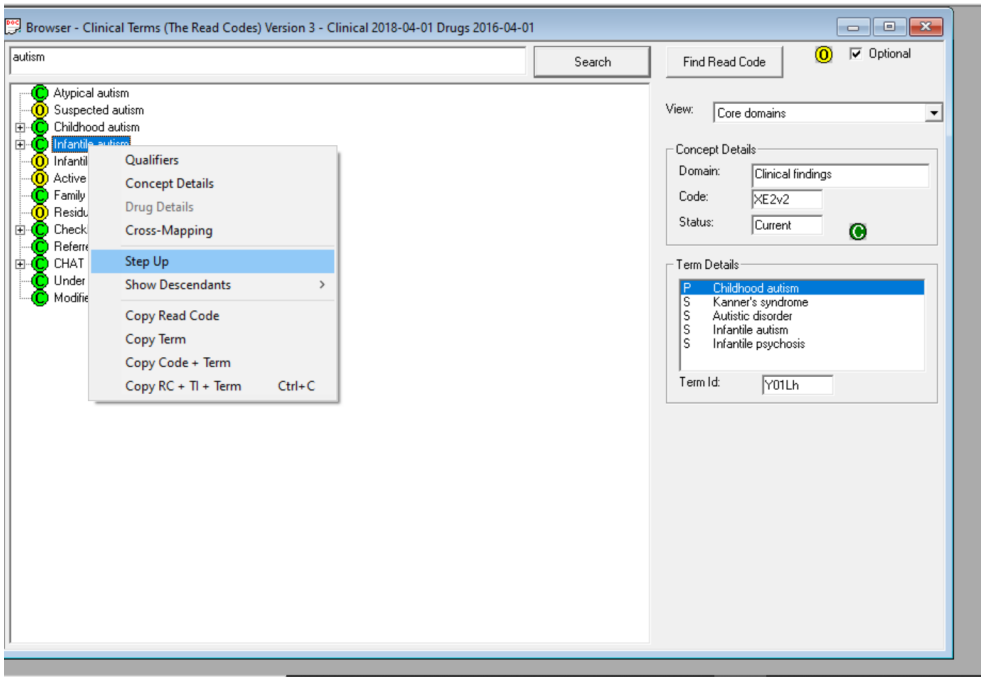
> 2. To develop a list of clinical codes for primary and secondary care which correspond to the signs, symptoms, and diagnosis of the developmental disorders listed in the NICE guideline for developmental follow-up of children and young people born preterm (NICE, 2017b)

Clinical codes are entered into children's records by their healthcare providers as part of their routine care. Children with a clinical code (see below) in their primary or secondary care records responding to the signs, symptoms, or diagnosis of one (or more) of these disorders were identified by the Born in Bradford data team. The BiB data team did not have access to the Child Development Centre (CDC) records. Diagnoses made in the CDC are routinely communicated back to primary care; primary care records have been used previously to identify children whose diagnoses will have been made in CDC and secondary care, although there will be some time lag (Masefield, Prady, Sheldon et al., 2022).

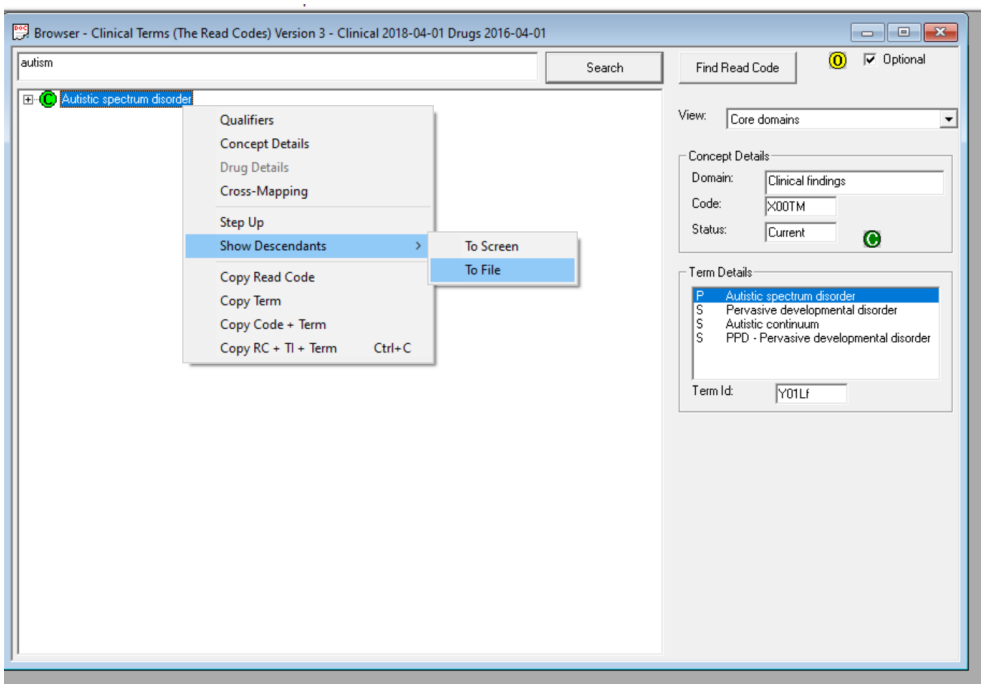
All the primary care practices in Bradford use "SystmOne" for their electronic patient records (Masefield et al., 2022). SystmOne records data using clinical codes called Clinical Terms Version 3 (CTV3), which are known colloquially as 'Read codes' (the initial version was devised in the 1980s by James Read (De Lusignan and Van Weel, 2006)). Secondary care data are recorded using the 10th version of the International Classification of Disease (ICD-10). Lists of CTV3 and ICD-10 codes representing the signs, symptoms or diagnosis of developmental disorders were developed in three stages:

1) Lists published in previous literature were found by searching both for developmental disorders generally, and each of the specific conditions in the NICE guideline (NICE, 2017b). The references for the sources used are shown in Table 25. Some published lists used a previous version of the clinical terms i.e. CTV2 (e.g. (Swann, Lone, Harrison et al., 2022)), in which case the Clinical Terminology Browser ("Read code browser") was searched for the corresponding term, and where possible the updated code was used. The Clinical Terminology Browser was downloaded from NHS TRUD (Technology reference update distribution), available here: https://isd.digital.nhs.uk/trud/user/guest/group/0/home

2) The Clinical Terminology Browser was searched for terms corresponding to developmental disorder and each of the specific disorders, and the 'step up' function, and the 'show descendants' functions were used to ensure all possible codes related to a disorder were included. For example, a search for 'autism' gives the following terms. There is the option to 'Step Up':



This shows that the parent term is 'Autistic spectrum disorder'. There is the option to 'Show Descendants' to file, which lists all of the terms which can be included:



3) NHS Digital's Classifications Browser ICD-10 5th Edition was searched in the same fashion for secondary care data (NHSDigital, 2011). This was a simpler process as ICD-10 has fewer coding options compared to CTV3 (De Lusignan and Van Weel, 2006).
4) Finally, lists were checked for completeness against list published on OpenCodelists, where available (Bennett Institute for Applied Data Science, 2022) .

Table 25 - Sources used in the process of building lists of CTV3 and ICD-10 codes relating to the signs, symptoms, and diagnosis of developmental disorders

Source - CTV3 codes	**Source - ICD-10 codes**
Cerebral palsy	
(Masefield, Prady and Pickett, 2021)	(Carter et al., 2019)
Opencode list (OpenSAFELY, 2022a)	(Swann et al., 2022)
Motor function problems	
(Masefield et al., 2021)	(Swann et al., 2022)
Opencode list (OpenSAFELY, 2022b)	
Learning disability (intellectual disability)	
(Masefield et al., 2021)	(Swann et al., 2022)
(Strategic Health Facilitation Team, 2018)	
Opencode list (OpenSAFELY, 2022b)	
Opencode list (OpenSAFELY, 2022c)	
SEND and educational difficulty	
(Masefield et al., 2021)	No relevant sources identified
Opencode list (OpenSAFELY, 2022a)	
Executive function problems	
No relevant sources identified	(Uysal, 2018)
Speech, language, and communication disorders	
(Masefield et al., 2021)	(Swann et al., 2022)
Opencode list (OpenSAFELY, 2022a)	
Attention, impulsivity, and hyperactivity (ADHD)	
(Swann et al., 2022)(this paper uses CTV2, but some of the codes were the same)	(Swann et al., 2022)
(Masefield et al., 2021)	(Kuan, Denaxas, Gonzalez-Izquierdo et al., 2019)
Autism Spectrum Disorder	

Source - CTV3 codes	**Source - ICD-10 codes**
(Masefield et al., 2021)	(Swann et al., 2022)
	(Kuan et al., 2019)
Emotional, behavioural (and social) problems	
Swann 2022 (this paper uses CTV2, but some of the codes were the same)	(Swann et al., 2022)
Feeding problems	
(Masefield et al., 2021)	No relevant sources identified
Visual Impairment	
(Lingam, Ellis, Naqvi et al., 2013)	No relevant sources identified
Hearing impairment	
(Lingam et al., 2013)	No relevant sources identified
Developmental delay	
(Masefield et al., 2021)	No relevant sources identified
General developmental disorder (unclassifiable)	
(Masefield et al., 2021)	(Swann et al., 2022)

The BiB data team only granted access to primary and secondary care events in relation to pre specified codes. Therefore, to mitigate against unusual coding practices the code list was initially very broad, and then later narrowed down, after discussion with stakeholders (see below). In order to be as inclusive as possible, the CTV3 codes include codes relating to diagnoses (e.g., "Cerebral palsy", "Dyspraxia", and "Attention deficit hyperactivity disorder"), as well as codes which related to signs or symptoms of a diagnosis (e.g., "Coordination problem", "Not yet walking" and "Unable to concentrate"). The final lists used are shown in appendix 4.2. These lists were given to the data team at BiB who returned a Stata file in long format, where each CTV3 or ICD-10 code was an observation, therefore there were multiple observations for some participants. The file also contained the date the code first appeared in the child's records. For the majority of the analyses, the first code (either CTV3 or ICD-10) which appeared in either the primary or secondary care record was recorded as the incident code.

Breastfeeding

Infant feeding practices have been shown to be associated with both gestational age, and developmental disorders (Pereyra-Elías et al., 2022; Nicole M. Hackman, 2016; Heikkilä et al.,

2011). Breastfeeding amongst the BiB cohort was thus explored. The possibility of using codes recorded in primary care records was explored. However, the *absence* of a 'breastfeeding code' might not reliably mean the child had not been breastfed. Consequently, all breastfeeding codes were removed from the dataset. An alternative method for determining whether a child was breastfed was explored, see Figure 58, box 9 .

Genetic Conditions and Syndromes

Several published lists included genetic conditions and syndromes such as Down syndrome, Fragile X-Syndrome, or Rett syndrome, for example (Swann et al., 2022; Masefield et al., 2021). These codes were included in the original lists requested from BiB. However, on review, in this context genetic conditions represent an 'exposure', not an outcome (Reilly, 2009). The list of codes which were later stage exclusions are shown at the end of the code lists in appendix 4.2.1 and 4.2.2.

Meeting with Community Paediatricians

On 11th December 2024 a meeting was held with eight of the Community Paediatricians in Bradford for their weekly 'Education Meeting' to present the methods and describe the development of the clinical code lists. On their suggestion any codes related to what could be temporary or transient problems were excluded. This is because, in order for the term "disorder" to apply, a developmental problem must be "persistent and pervasive" (NICE, 2017b). This led to the removal of several codes, for example those related to temporary hearing loss (such as "Hearing difficulty", "Hearing loss", "Hearing problem"). Codes which related to sensorineural hearing loss or deafness (such as "Partial deafness", "Bilateral deafness", "Sensorineural hearing loss, bilateral") were retained. This also correlates with the NICE guidelines, which defines hearing impairment as "profound deafness or impairment severe enough to need hearing aids or cochlear implant" (NICE, 2017b). Other examples of codes excluded after this meeting included "Other transient visual loss", "Other visual discomfort" and "Other visual distortion". These had initially been included via published lists in the literature but were felt not to reflect the outcome measure as previously defined. All excluded codes are shown in appendix 4.2.1 and 4.2.2.
The community paediatricians also provided their thoughts on categorisation of codes. For example, they advised that the CTV3 term "Learning difficulties" should not be categorised with the "Learning disability" outcome group and would be better categorised as "Education problems", since learning difficulties such as dyslexia, do not affect intellect, whereas people with learning disabilities by definition have intellectual impairment (Mencap, 2023). These suggestions were implemented.

3.4.2.2. The outcome measure – education records

The systematic review showed that the majority of UK research exploring developmental outcomes of children born before full term use educational attainment or SEND as the outcome measure but it was unclear to what extent developmental disorders and educational outcomes intersect. In addition, parents' ability (or desire) to seek medical advice if they have a concern about their child's development may be influenced by their social, cultural, or ethnic background (Lindquist et al., 2015; Dixon-Woods et al., 2006; Scheppers et al., 2006; Szczepura, 2005). Therefore, educational records were used in conjunction with medical records, to reduce the possibility of 'missed' cases.

Schools have an obligation to report the number of children with SEND annually in the school census. BiB receives data annually from all state-funded schools in Bradford, including special schools (for children whose needs cannot be met in mainstream school). For each academic year (where data were available) a child was classified as:

1. Having an Education, Health and Care Plan (EHCP)
2. Receiving SEND Support
3. Having a Statement
4. Receiving School Action Plus
5. Receiving School Action
6. Not having SEND

School action, school action plus and 'statements' are outdated terms, used prior to the Children and Families Act 2014. School action was the lowest level of support, where the school had made 'in house' adjustments to meet the child's needs. School action plus meant advice or support was received from outside agencies or professionals, such as speech and language therapy or an educational psychologist. The highest level of support was previously a "statement"; a legal document specifying a child's additional needs and extra support they require. Statements have been phased out and replaced by EHCPs. The categories 'School Action' and 'School Action Plus' were combined and replaced by "SEND support" (Hatton and Emerson, 2016).

The BiB data team sent a file with the SEND status (1-6 above) for each participant for each academic year. BiB do not have access to any more granular data on the specific reasons for children having SEND, so the analyses which could be conducted were limited. However, some inferences may be made based on nationally available data, which shows the most common reasons for having an EHCP (autism; speech, language and communication needs; social, emotional and mental health), and then for SEND support (speech, language and communication

needs; social, emotional and mental health; learning difficulty), see bar chart below (Figure 56). For consistency with the health data, the first time the child was recorded as having any type of SEND (including EHCP, SEND support, statements, school action or school action plus) was used to calculate cumulative incidence and incidence rate. This is in accordance with other studies using BiB data (Atkinson et al., 2022) and studies using other cohorts, e.g. the Millenium cohort study, where "parents were asked whether the school or local education authority had ever told them their child has SEN" (Alterman et al., 2021).

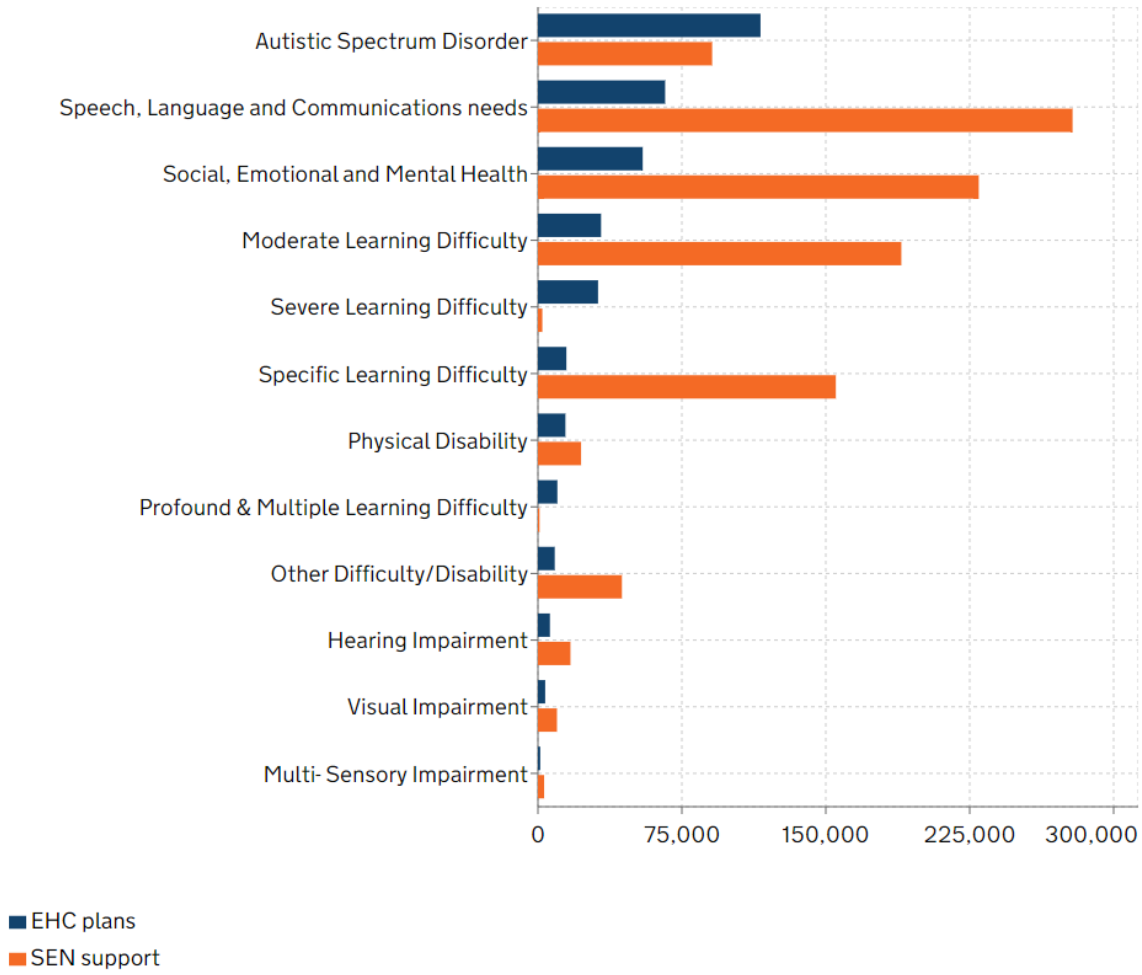


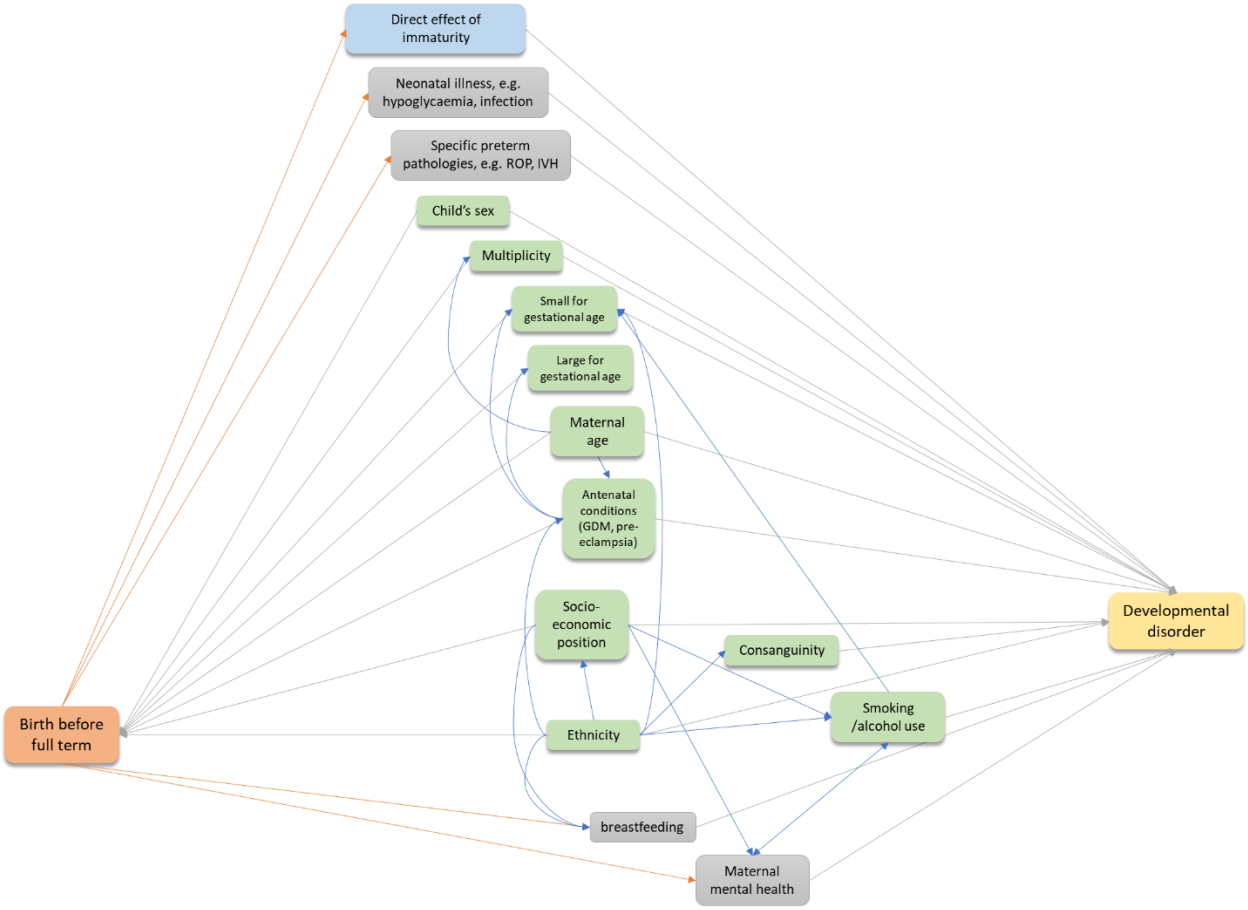
Figure 56 - Number of pupils with an Education and Health Care Plan or Special Educational Need support, by type of need, 2002/23 (GOV.UK, 2023)

EHC plans = Education and Health Care Plans; SEN support = special educational need support

3.4.3. Covariates of interest

Figure 57 is a figurative representation, introduced in Chapter 1: Background, of the putative relationships between the exposure (gestational age), the outcome (developmental disorder), and potential confounders and mediators.

Figure 57 - Figurative representation showing possible associations between exposure (birth before full term), outcome (developmental disorder) and co-variables



Orange box = independent variable; yellow box= dependent variable; grey boxes= possible mediating variables; blue box = direct effect of immaturity; green boxes = possible confounders; blue arrows = connection between covariate; orange arrows = covariates which may be influenced by birth before full term. ROP: Retinopathy of Prematurity. IVH: Intraventricular Haemorrhage

- **Neonatal factors**
    - Neonatal illness: using admission to SCBU as a proxy marker for neonatal illness was considered.
    - Specific preterm pathologies: data was not available
    - Child's sex
    - Multiplicity
    - Small for gestational age (<10th centile)
    - Large for gestational age (>90th centile)
- **Antenatal factors**
    - Mother's age at the baby's delivery

  - Pre-eclampsia
  - Gestational diabetes
  - Type of labour onset: spontaneous delivery has been used in existing literature as a proxy marker for absence of pregnancy complications (Alterman et al., 2021), i.e. induction of labour or caesarean section would suggest there had been antenatal concerns such as pre-eclampsia, or GDM. It was decided that this approach was not viable here; considering that elective caesareans are often carried out for reasons such as having had a previous caesarean, maternal request, or breech presentation, none of which suggest any antenatal concerns about the current pregnancy (Gholitabar, Ullman, James et al., 2011).
  - Maternal smoking during pregnancy

- **Socio-economic factors and ethnicity**
  - Socio-economic position (SEP): The intersection between SEP with ethnicity within Bradford creates some challenges for measuring SEP accurately. Employment norms vary between ethnic groups: in the BiB cohort 8% of White British mothers have never been employed, compared to 49% of Pakistani mothers (Fairley, 2010). The Index of Multiple Deprivation (IMD) can be used to measure poverty, but in Bradford it is unlikely to pick up variation in SEP since such a large proportion Bradford is deprived (Wright et al., 2013). Therefore, subgroups derived from a latent class analysis (LCA) of the BiB cohort were used, which used 19 measures of SEP to define five subgroups of women for all ethnicities with similar socio-economic positions (Fairley et al, 2014). Whilst this approach is well suited to Bradford's population, it may make findings less generalisable. Therefore, in addition to the five group LCA more generalisable measures of SEP, namely maternal education and receipt of means tested benefits (MTB) were also used, in a sensitivity analysis.
  - Child's ethnicity: BiB collected 16 group ethnicity and five group ethnicities (see Table 26).
  - Consanguinity

Table 26 - Categorisation of ethnic groups within the Born in Bradford cohort

White	Mixed	Asian	Black	Other
English, Welsh, Scottish, Northern Irish	White and Asian	Pakistani	African	Any other ethnic group
Irish	White and Black African	Indian	Caribbean	
Any other White background	White and Black Caribbean	Bangladeshi	Other Black, African or Caribbean background	
	Any other Mixed background	Chinese		
		Any other Asian background		

16 group ethnicity = white boxes; 5 group ethnicity = column titles

- **Postnatal factors:**
    - Breastfeeding
    - Maternal mental health

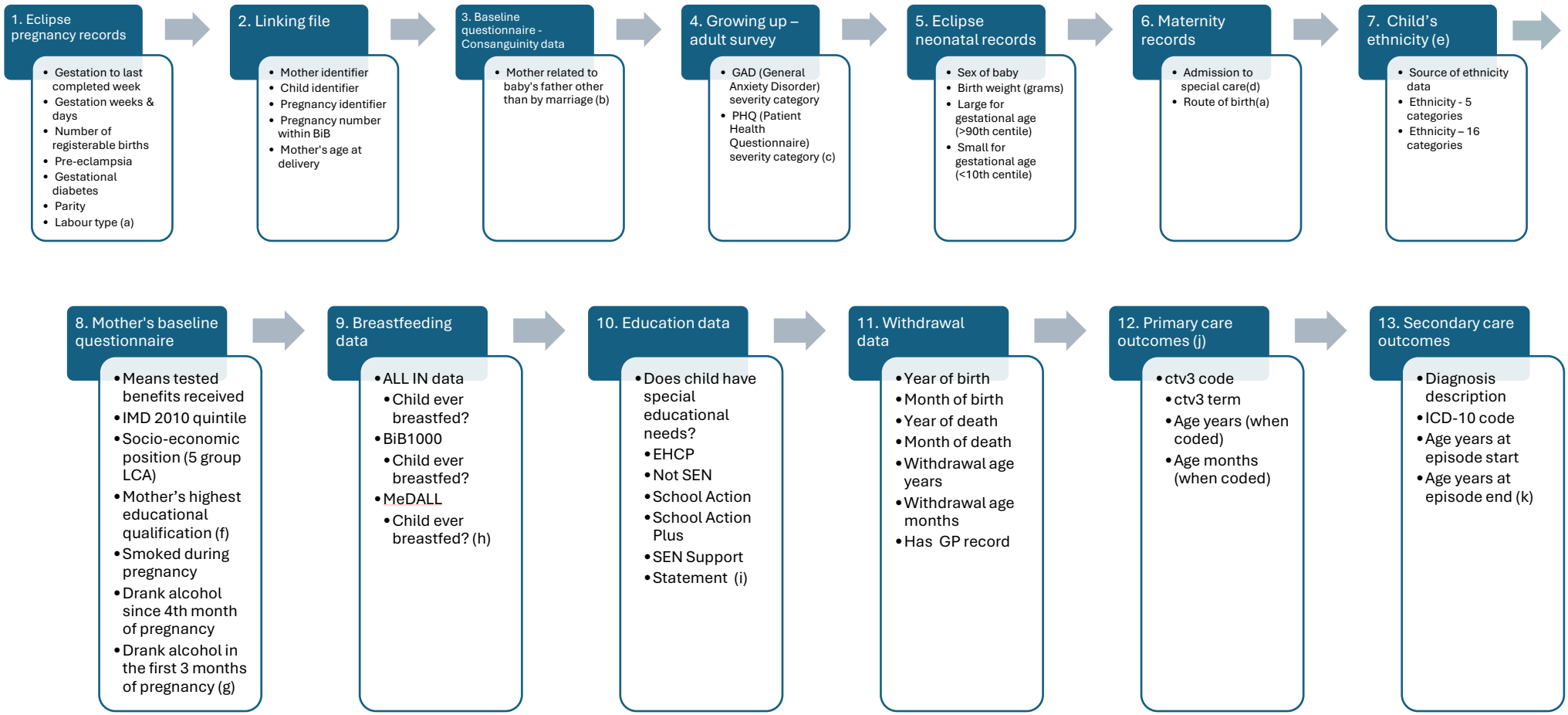
3.5. Data manipulation

Data preparation was undertaken in Stata/SE software version 18 (StataCorp, 2023).

3.5.1 The data files

Before carrying out any data analyses files were merged and reformatted into an analysis file by sequentially adding data to the mothers' pregnancy records, as shown in Figure 58.

Figure 58 - Creation of analysis cohort



Blue box: file name, white box: variables used. Notes (a)-(k) explained on following page.

Key for figure 58:

(a) These variables appeared contradictory in some cases, e.g. some children recorded as spontaneous deliveries were also recorded as being delivered by elective caesarean section. Therefore, neither variable was used further.

(b) Where the response was 'don't know' (fewer than 10 participants) this was recoded to missing to avoid very small numbers within groups.

(c) The "moderately severe" and "severe" groups were combined into "Moderately severe and severe symptoms".

(d) Where the response was 'don't know' (27) this was recoded to missing

(e) In the majority of cases (84.5%) this was derived by BiB from the child's education record

(f) Foreign unknown and Other were combined into a single category to reduce the possibility of very small numbers within groups, and "Don't know" (129 participants) was changed to missing.

(g) Recoded as follows:

- "Yes, once a week", "Yes, occasionally", "Yes, not specified" all recoded as "yes"
- "Don't remember" changed to missing
- "No", unchanged

(h) Information on breastfeeding was collected for three sub cohorts MEDALL, AllIn and BiB1000. A participant could be in more than one of these sub cohorts. Where there were multiple entries for a child, the observation taken closest to baby's birth were retained, in this case BiB100 (carried out at 6 months of age).

(i) An "ever any SEND" variable was derived by coding any type of SEN support i.e., number 1, 3-6 above as "ever SEND". This process was repeated for an 'ever EHCP' variable if ever recorded as having an EHCP or statement of special educational needs.

(j) Three sources (GP, health visitor, child health) were merged. Each CTV3 code was on a separate row. Some codes were recorded at an implausibly young age, in which case the age at diagnosis was replaced with missing, for example:

- "Unspecified mental retardation" & age_months <6
- "Learning disability" & age_months <6
- "Developmental delay" & age_months <1

(k) Contained only inpatient data. An episode describes the healthcare activities making up a 'spell', which is the whole period of time the patient spends in secondary care (Royal College of Physicians, 2015).

3.5.2 Exclusion and inclusion criteria

In order to be included in the analysis cohort, the mothers' Eclipse pregnancy record, which contained data on gestational age, and the linked primary care records for the child were required; any child with missing primary care records or missing gestational age was excluded. Any multiple births of a higher order than twins were excluded, to reduce possible deductive disclosure. A subgroup of the analysis cohort was created, which had linked education records (see Figure 59, chapter 4).

3.5.3 Data exploration, cleaning, and description

Once the files had been merged, and the prespecified exclusion and inclusion criteria were applied, the data were explored, cleaned, and described. An excel file was created manually combining results from a sample of participants to ensure there was not an error with the coding, and in particular that the linkage with maternal data and that the incident diagnosis was preferentially retained in each case. The number and age of children who either died or withdrew from the study were described. All of the diagnoses were tabulated and checked to ensure they corresponded to the code lists sent to BiB, and whether any codes not related to developmental disorder had erroneously been included.

Age at first code

Developmental disorders can be defined as "A group of problems that become apparent during child development" (NICE, 2017b) and therefore are not diagnosed in the neonatal period; the exception being sensorineural hearing loss, which is screened for shortly after birth (GOV.UK, 2013). For example, cerebral palsy is typically diagnosed between 12 -24 months (Te Velde, Tantsis, Novak et al., 2021), ASD between 38 - 120 months (van 't Hof, Tisseur, van Berckelear-Onnes et al., 2021). Therefore, any codes (related to any condition) which were recorded before 12 months of age were reviewed carefully and discussed with supervisors. In addition, some conditions are only 'pathological' if they occur after a certain age, and so if the occurred before a certain cut off would be dropped, specifically:

- "Nonorganic encopresis" and age <5 years
- "Not yet toilet trained" and age <5 years
- "Unable to write" and age <5 years

In the systematic review a broader approach was used, where papers which recorded outcomes before 2 years of age were routinely excluded. Due to the disparity in approaches an exploratory

analysis was undertaken, where all incident codes which occurred before 2 years of age were removed, and the cumulative incidence recalculated.

Whereas conditions which were likely to have been coded at the incorrect time had the time at diagnosis changed to missing, i.e.:

- "Unspecified mental retardation" and age <6 months
- “Learning disability" and age <6 months
- "Developmental delay" and age <1 month
- "Cerebral palsy" and age <6 months

This meant that when the data were sorted by age at diagnosis prior to dropping duplicate participant IDs, the diagnoses where the age at diagnosis was missing would be placed last if the child had another diagnosis recorded, and therefore dropped.

Feeding problems

In order not to include children who were having difficulty establishing feeds in the newborn period, as opposed to children with oro-motor feeding difficulties as described by NICE, codes relating to feeding problems (e.g., "Feeding difficulties & mismanagement" or "Feeding difficulties and mismanagement") that were recorded before 6 months of age were dropped.

Description

The characteristics of the resulting analysis cohort were compared to the whole cohort.

3.6.1. Statistical analysis 1

These statistical analyses were carried out in Stata/SE software version 18 (StataCorp, 2023).The analyses were designed to meet objectives 3 -5 :

3. To determine the cumulative incidence and incidence rates of any developmental disorder, and of individual developmental disorders, in the Born in Bradford cohort
4. To explore how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity
5. To investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models

3.6.1.1. Determining the cumulative incidence of any developmental disorder in the Born in Bradford cohort (part of objective 3)

Study period and participant age

The child participants were born between 2007 and 2011. The participants' birth month and year were recorded. In order to calculate an approximate age, all days of birth were set to the first of each month, for example all the participants born in January 2008 were given a date of birth of 01/01/08. In order that all the participants had the same exposure time a cut-off point was used. The most appropriate cut-off point was decided by determining the participants' age at the point of data extract (see section 4.6. Participant age and academic year at data extract).

Medical records

The cumulative incidence of a code corresponding to a sign, symptom or diagnosis of any developmental disorder in primary care, secondary care or either records was calculated by dividing the number of new cases of the outcome of interest during the study period by the total number of children at risk of the outcome at the start of the study (Rassen, Bartels, Schneeweiss et al., 2018). Exact binomial 95% confidence intervals were calculated, unless otherwise specified.

Education Records

As with the medical records, the most appropriate cut off point (in terms of academic year group) was decided by determining the last school year with minimal missing data. The cumulative incidence of SEND and EHCP up to and including Year 7 of school were calculated using the same methods as above for developmental disorder.

Venn diagrams were created to show how the numbers of children with a diagnosis from secondary care, primary care and special educational needs or EHCPs overlap. Descriptive statistics were used to compare the population with and without a developmental disorder in medical or education records (i.e., SEND) according to covariates of interest.

3.6.1.2. Determining the incidence rate of any developmental disorder in the Born in Bradford cohort (part of objective 3)

Medical records

The date of data extract for primary care was 02/02/2023 and for secondary care was 24/05/2023. There were six children who received their first secondary care code in the time between the primary and secondary care data extract, however, they had all already received a primary care diagnosis by that time. For the calculation of incidence rate for medical diagnoses a participant contributed person time from their date of birth (approximated as above) to the date of the first relevant code appearing in their primary or secondary care record (whichever occurred sooner), or until the date of their death or withdrawal or until the 02/02/2023 if none of these occurred. Once the years exposed were calculated the *stptime* commands were used in Stata to compute the person-time and incidence rate, after having used the *stset* command to declare the data to be survival time data. *Stptime* calculates confidence intervals "using the quadratic approximation to the Poisson log likelihood for the log-rate parameter" (StataCorp, 2013).

Education Records

The Born in Bradford team receive information on SEND status on 31st July each year from the local authority. BiB were not able to specify when within the school year the data is collected by schools. Therefore, a midyear point of 1st March was used for the calculation of incidence rate. As with the medical records a participant contributed person time from their date of birth (approximated) to the date of the first time they were recorded as having any type of SEND, or until the date of their death or withdrawal or until the last academic year we have data for (i.e., year 7, 8, 9 or 10) added to their age at school entry, plus 6 months to account for the mid-year

point at 'diagnosis' as described above if none of these occurred. The *stset* and *stptime* commands were then used as above to calculate incidence rate and associated 95% confidence intervals.

3.6.1.3. Exploring how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity (objective 4)

The cumulative incidence and incidence rate of developmental disorders from medical records were stratified according to the characteristics in 3.4.3. Covariates of interest. This was repeated with education records for SEND.

3.6.1.4. Investigating how the cumulative incidence of developmental disorders varies according to gestational age using regression models (objective 5)

Gestational age and developmental disorder

A set of exploratory analyses were undertaken investigating the relationship between gestational age and developmental disorders (from medical records), and then repeated separately for SEND from education records. The following options were explored as per Richards et al. (Richards et al., 2016a):

(1) categories for each week comparing to a 40-week referent category,
(2) categories of prematurity, akin to those recommended by the ACOG comparing to a full term (39-41 weeks) referent category (Coathup, Boyle, Carson et al., 2020; Quigley et al., 2012a)
(3) a continuous (linear model),
(4) as above (3) but adding a quadratic term (i.e., squared gestational age).

The model which best fit the data and allowed easiest interpretation by clinicians was chosen for on-going analyses.

Creating the logistic regression model for developmental disorder

Next the covariates were added to both models (developmental disorder from medical records, and SEND from education records):

- a measure of socio-economic position: first the 5 group LCA, and then this was replaced with maternal education and receipt of means tested benefits in a sensitivity analysis, see below
- Child's ethnicity
- Child's sex
- Antenatal feto-maternal health, measured by SGA, GDM, pre-eclampsia

This was performed in two stages, initially a complete case analysis, which excluded any children who had missing data for any of the above covariates. Following this, missing data was explored as described earlier, and then multiple imputation by chained equations was used. Interactions between gestational age and the other covariates were considered and explored using likelihood ratio tests. The model fit was determined using Pseudo R2, Hosmer-Lemeshow chi2 and classification tables.

Model Diagnostics

Collinearity was investigated by inspection of correlation coefficients and Variance Inflation Factors (VIF). Outliers, high leverage points or highly influential points were investigated. If the assumptions were in doubt, then the model was re specified.

Sensitivity analyses

Two sensitivity analyses were carried out:

1. The cumulative incidence of developmental disorder was calculated using a restricted case ascertainment strategy, first excluding codes related to sleep apnoea, as the inclusion of this within the outcomes was queried during the peer review process for the systematic review paper, and then restricted further to using only using diagnostic codes corresponding to DSM-IV or ICD-10 developmental disorders (i.e. excluding codes related to developmental 'problems', signs, or symptoms). The codes which were included in this restricted definition are indicated in table of code lists (see appendix 4.2). The relationship between this restricted outcome and gestational age was then modelled in the same way as previously described.
2. The imputed multivariable regression model was repeated using maternal education and receipt of means tested benefits as an alternative measure of socio-economic position.

Stratified analyses by ethnicity

The complete case analysis and the analysis using imputed data were then repeated stratified by the two largest ethnic groups in the cohort (White, Asian).

Missing Data

It was not possible to independently verify the completeness of primary or secondary care records; it is possible that codes were not recorded correctly, or at all, in which case the child would not be recorded as a 'case'. It is also possible that children could have had inpatient stays in other hospitals which BiB did not have access to linked records for and Bradford Teaching Hospitals NHS Trust does not have all tertiary paediatrics services .

The proportion of missing data for each variable was calculated. Patterns of missingness were explored using summary statistics and cross tabulations with background characteristics. There are three mechanisms by which data can be missing from a data set, as defined by Rubin (Rubin, 1976).

1. Missing Completely At Random (MCAR): the cause of the missingness is neither the (unknown) missing data, nor the observed data. Data which is MCAR will result in a smaller sample size, but will not cause biased results, since the non-missing data is representative of the (unavailable) complete dataset (Jakobsen, Gluud, Wetterslev et al., 2017).
2. Missing At Random (MAR): Other variables within the dataset can predict the missingness of the missing variable, but the missingness does not depend on the value of the missing observation itself (UCLA: Statistical Consulting Group, 2021; Azur, Stuart, Frangakis et al., 2011).
3. Missing Not At Random (MNAR): the likelihood of an observation being missing is related to the true (unknown, missing) value of that observation itself (Carpenter and Smuk, 2021).

Following review of the analysis cohort, the most likely missing data mechanisms were considered. The potential methods for dealing with missing data were: complete case analysis, simple imputation, and multiple imputation.

Complete Case analysis

Complete case analysis may be appropriate if there are <5% missing data, and if the data are missing completely at random (Jakobsen et al., 2017; Pedersen, Mikkelsen, Cronin-Fenton et al., 2017; Azur et al., 2011). Due to the reduced sample size, complete case analysis results in loss of power, and may result in biased estimates if the data is not MCAR (Azur et al., 2011).

Simple Imputation

This allows the whole dataset to be used, even where there are missing values. Simple (also known as single) imputation is straightforward to implement but is not an ideal solution, largely because it artificially reduces variability in estimates, so will likely lead to results which are too precise (Azur et al., 2011). There are three types of simple imputation:

- Mean imputation (also known as mean substitution): where the missing values are replaced by the mean of that variable (Johnson and Young, 2011).
- Missing as a separate category: a new category corresponding to the missing values is created. This can only be used for categorical data (Storvik 2013).
- Similar value imputation: Imputing the missing values with one from another participant which most closely matches the participant with missing data.

Multiple Imputation

In multiple imputation, numerous datasets are created, where the missing values are filled slightly differently each time, based on the non-missing data available for each individual. The analyses of data which have been multiply imputed takes into account uncertainty and results in standard errors which are accurate, because of the multiple predictions created for each missing value (Azur et al., 2011). Multiple imputation is more efficient than complete case analysis as it allows data from all cases to be used and does not result in artificially precise results as in simple imputation. Therefore, for the regression analyses multiple imputation for missing values was used. There are two types of multiple imputation, both of which assume the missing values are MAR (Johnson and Young, 2011). The first, a 'multivariate normal' model, uses Markov Chain Monte Carlo (MCMC) procedures, and requires all variables in the model to be continuous with a multivariate normal distribution (UCLA: Statistical Consulting Group, 2021; Johnson and Young, 2011). The alternative is Multiple Imputation Chained Equations (MICE), also known as sequential regression multivariate imputation, which allows each imputed variable to have a separate conditional distribution; this was the approach taken for the regression analyses, since several of the variables are not continuous and there are several variables with missing data requiring imputation (Azur et al., 2011; Johnson and Young, 2011). In MICE, all missing data are initially replaced by a simple imputation, to act as "placeholders". Then, the variables with missing data in turn have their missing data replaced by results of regression, set to whatever type of regression is appropriate to that variable, i.e., linear regression for continuous variables, logistic regression for binary variables, multinomial logistic regression for unordered categorical variables (e.g.

ethnicity), ordered logistic regression for ordered categorical variables (e.g. maternal education or IMD). The 'first' variable with missing data is the dependent variable, and all the other variables to be included in the model, including the outcome variable for the final analysis regression (i.e., in this case developmental disorder), as well as auxiliary variables (which may not be included in the final regression model, but could be related to the missingness of the other variables – see below). This is then repeated (automatically) for the second variable with missing data, except that this time the first variable (now an independent variable, in the regression of the second variable with missing data) contains observed and imputed values, which resulted from the first variable's regression. When all the variables with missing data have had their missing data 'replaced' with results from the regressions, the first 'cycle' is complete. The cycles are then repeated a specified number of times, and the imputations are updated each time (UCLA: Statistical Consulting Group, 2021). MICE relies upon data being MAR or MCAR; if data is MNAR MICE should not be used (White and Carlin, 2010). Unfortunately, there is not a simple single test to distinguish between data being MAR or MNAR (Molenberghs, Beunckens, Sotto et al., 2008).

Auxiliary variables

Auxiliary variables are variables which are not included in the final analysis model but may hold information about missing data. Auxiliary variables can reduce the standard error for the estimates for the analysis model and therefore improve the imputation (Johnson et al., 2011 (Johnson and Young, 2011). Auxiliary variables were considered based on the previous literature and knowledge of the topic. In addition, potential auxiliary variables were investigated by examining their correlation with missingness. A set of missing data flags were created for each variable with missing data to be imputed. These binary flag variables were then used in regression models, where the binary flag was the dependent variable, and the potential auxiliary variable was the independent variable, to determine if the potential auxiliary variables were significantly different in those with missing data compared to those without. Including auxiliary variables in the imputation model increase the plausibility of the MAR assumption, if they are good predictors of missingness.

Imputation Diagnostics

The relative increase in variance (RVI), fraction of missing information (FMI), degrees of freedom (DF), and relative efficiency (RE) were explored. The distribution of the imputed and observed values were compared to check the plausibility of the results of the imputation.

3.6.1.5. Determining the incidence rates of individual developmental disorders in the Born in Bradford cohort (part of objective 3)

Grouping developmental disorders

A list of clinical codes present within the analysis cohort was generated, and then split into fourteen categories according to the developmental disorders listed by NICE, plus an additional group for codes which related to generic developmental disorder and could not be categorised further. This grouping was done based on existing published lists where possible, in accordance with the hierarchical structure of the CTV3 codes, ICD-10, and in discussion with paediatricians.

3.6.1.6. Exploring how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity (objective 4)

The age at which a code corresponding to one of the developmental disorders first appeared in the medical (either primary or secondary) records was calculated and plotted on histograms.

The incidence rate of each developmental disorder was calculated, as described above in section 3.6.1.2. The incidence rate of each developmental disorder according to gestational age categories was calculated. Finally, the incidence rate of each individual developmental disorder was calculated separately for the two largest ethnic groups within the cohort.

3.6.2. Statistical analysis 2

Analyses were undertaken in Stata/SE software version 18 and R version 4.3.2 (R Core Team, 2023; StataCorp, 2023); data preparation and multinomial regression were carried out in Stata as above and latent class analysis was undertaken using the poLCA package in R (Linzer and Lewis, 2011), multinomial regression was carried out in Stata. These analyses were designed to meet objectives 6-7:

6. To carry out a latent class analysis to identify profiles of developmental outcomes
7. To determine which factors are associated with different profiles of developmental disorders

3.6.2.1. Carrying out a latent class analysis to identify profiles of developmental outcomes (objective 6)

Latent class analysis (LCA) uses observed data (manifest variables) to uncover hidden (latent) groups or "classes" within populations (Miettunen, Nordström, Kaakinen et al., 2016; Oberski, 2016). The classes which are generated are determined based on the probability of each category of each variable being observed in a participant within the population (Jung, 2008). Two commonly used alternative methods to classify groups within data are:

1. k-means clustering: requires the number of classes to be specified in advance, so is called a "supervised technique" (Soetewey, 2020)
2. Hierarchical clustering: can be used where the number of classes is not known in advance (an "unsupervised technique"), it helps to estimate the optimum number of classes (Soetewey, 2020)

LCA is more flexible and accurate than either of these techniques (Petersen, Qualter and Humphrey, 2019; Oberski, 2016; Schreiber and Pekarik, 2014). The optimum number of classes is unknown in the planned analysis, therefore k-means clustering is not an appropriate technique. Hierarchical clustering is also not ideal as it may group data which seem similar without taking into account information from other data points (Schreiber and Pekarik, 2014).

LCA uses maximum likelihood estimation, which results in classes which are internally homogenous but also heterogenous from each other, meaning that other factors (such as gestational age) which may increase or decrease the likelihood of belonging to a group can be investigated (Petersen et al., 2019; Berlin, Williams and Parra, 2014). LCA also provides fit

statistics, which can be used to help choose the best model for the data (Petersen et al., 2019; Rhead, Elliot and Upham, 2018; Miettunen et al., 2016; Vermunt, 2002).

LCA was undertaken using the following steps:

The latent class indicator variables were all the developmental disorders listed by the 2017 NICE guideline for follow up of preterm children and were included as variables in the analysis. These were already binary "0" or "1" for the analyses described above, and were recoded as "1" and "2" respectively for the LCA as required in R. As with the calculation of cumulative incidence, any incident diagnoses which occurred after a child's (approximated) 12th birthday were not included.

Class enumeration

A seed was set prior to analysis to ensure results could be replicated (Wardenaar, 2020). First, a one-class model was undertaken to act as a comparative baseline, followed by four additional models including one extra class each time (Weller 2020). To avoid convergence on a local solution (rather than a global solution) ten repetitions were performed with different starting values (Nylund-Gibson 2018). Higher maximum iterations of 3,000 and 8,000 were set for the four and five class models respectively (the default is 1,000) to ensure enough iterations of the estimation algorithm to find a solution (Linzer and Lewis, 2011).

The fit was evaluated using the Akaike information criterion (AIC), Bayesian information criterion (BIC), consistent Akaike's (CAIC), sample-size adjusted BIC (SABIC), with lower values indicating a better fit across all metrics (Weller, Bowen and Faubert, 2020).

Relative entropy and average posterior class probability were calculated and evaluated (Qiu, 2022), with values >0.8 and >0.7 considered acceptable respectively (Yu, Haynie and Gilman, 2024; Anthony, Scourfield, Moore et al., 2023; Qiu, 2022; Weller et al., 2020; Nylund-Gibson and Choi, 2018). Entropy is a measure of how accurately the model delineates classes (Anthony et al., 2023); average posterior class probability measures the accuracy of predicting participants' class membership (Nylund-Gibson and Choi, 2018). The optimal solution was chosen based on the fit statistics, entropy, and the posterior probabilities. According to the maximum posterior probability, children were classified into latent classes (Anthony et al., 2023).

When the optimal number of classes had been selected, the profiles of disorders were described and named in collaboration with paediatricians.

3.6.2.2. Determining which factors are associated with different profiles of developmental disorders (objective 7)

Multinomial logistic regression was used to predict latent class membership relative to the reference group, based on the covariates used in the multivariable regression model described above. The multinomial regression was carried out in in Stata/SE software version 18 (StataCorp, 2023) as per section 3.6.3, except using multinomial logistic regression instead of binary logistic regression. Multiple imputation by chained equations was used to manage missing data, as described towards the end of section 3.6.1.4.

There is an alternative to this two-stage approach, where the LCA is carried out, children are assigned to classes, and then associations are investigated separately. The covariates of interest, which may influence the probability of a child belonging to each latent class, could have been included in the LCA at the point the LCA is estimated. This one step method can be referred to as "latent class regression" (LCR); "latent class models with covariates" or "concomitant-variable latent class analysis" (Linzer and Lewis, 2011). There is disagreement in the literature about the "best" approach. The proponents of this method state that it is less likely to produce biased coefficients (Linzer and Lewis, 2011). However, identifying the class model first then adding covariates separately is now seen as preferrable (Weller et al., 2020), as the one step method can alter size and type of the latent class formation and invalidate results (Nylund-Gibson and Choi, 2018; Rhead et al., 2018; Asparouhov and Muthén, 2014). It also allowed exploration of the profiles of developmental disorder separately from their association with gestational age, which was considered to make the results more widely relevant.

3.7. Chapter summary

This chapter has described the methods used to meet objectives 2 -7 as laid out in chapter 1. The Born in Bradford longitudinal birth cohort was introduced. The derivation of the analysis cohort was described. The variables used were described. The methods for data manipulation and statistical analyses were detailed and justified. The following three chapters describe the results of these analyses.

Chapter 4: Results 1 - Descriptive Statistics and the Incidence of Developmental Disorders in the Born in Bradford Cohort

4.1. Introduction

The results presented in this chapter correspond to the third objective of the thesis:

> 3. To determine the cumulative incidence and incidence rates of any developmental disorder, and of individual developmental disorders, in the Born in Bradford cohort

First, in section 4.2, the selection of the analysis cohort is explained. There follows a description of the missing data on the key covariates (section 4.3). Descriptive statistics for the participants, according to the key exposure, gestational age, are presented (section 4.4). The relationship between ethnicity and other covariates is investigated (section 4.5). After determining the children's ages and academic year groups at the point of the data extract (section 4.6), the cumulative incidence and incidence rates of any developmental disorder (as a binary outcome) are presented in sections 4.7 and 4.8 respectively. The incidence rates of individual developmental disorders are explored in section 4.9. In order to facilitate comparison with national figures, the prevalence of SEND in educational records was calculated and is presented in section 4.10. The chapter ends with a sensitivity analysis, using a restricted case definition (section 4.11).

4.2. Selection of the analysis cohort

As described in Chapter 3, selection of the analysis cohort was based on the following criteria. Inclusion criteria were:

- non-missing gestational age in the mothers' Eclipse pregnancy record,
- linked primary care records for the child.

Exclusion criteria were:

- multiple births of a higher order than twins

There were 13,858 births in the BiB cohort, 332 were missing gestational age, 345 had no linked primary care record, and nine were part of multiple births higher order than twins. This resulted in an analysis cohort of 13,172 children (Figure 59). There was a smaller subset (11,492) of children within the analysis cohort with linked education records. A comparison of the analysis cohorts to the whole cohort, according to key characteristics are presented in Table 27 - Table 30. The analysis cohorts and the whole cohort had a similar distribution of most characteristics apart from multiplicity, as a result of the pre-stated exclusion criteria.

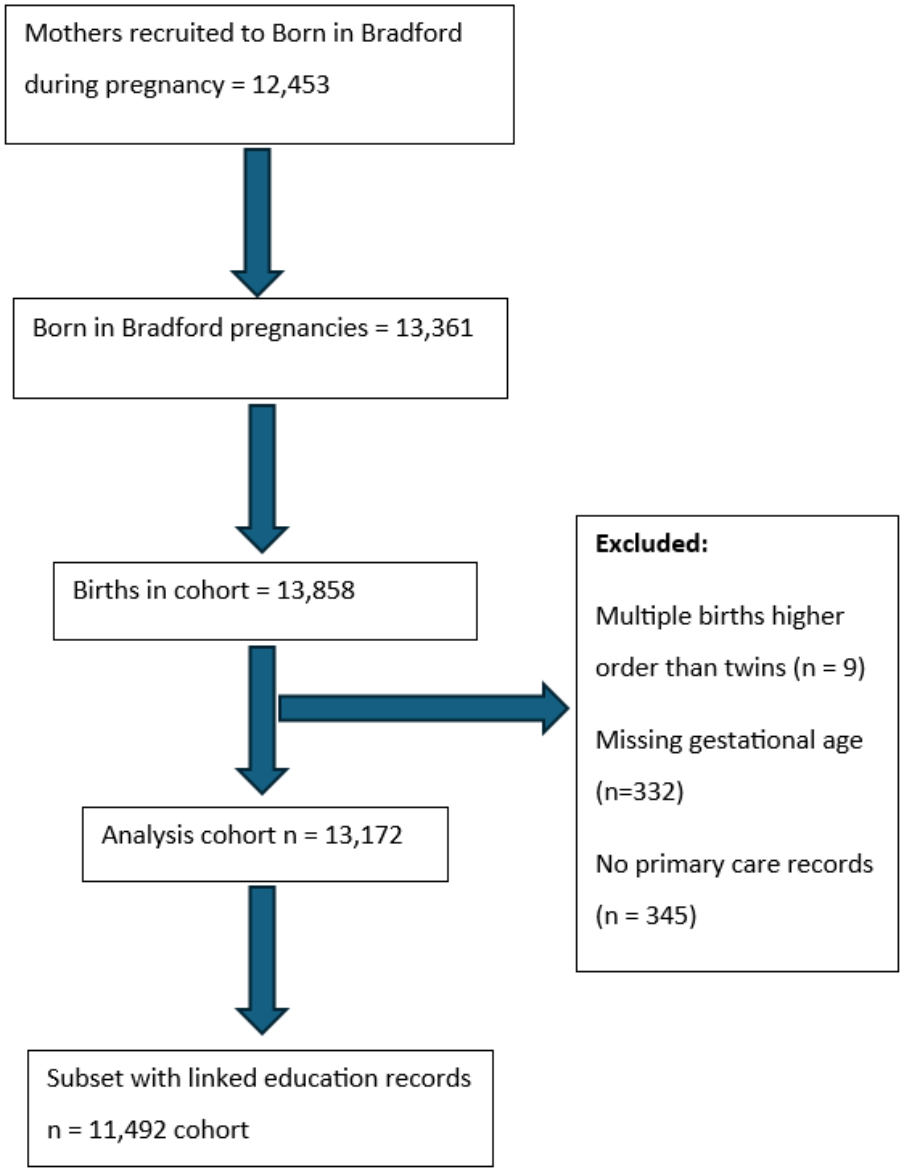


Figure 59 - Flow chart for selection of analysis cohort

Table 27 - Comparison of whole cohort, analysis cohort, and subset with linked education records based on neonatal characteristics

Characteristics	**Whole cohort (n = 13,858)**		**Analysis Cohort (n = 13,172)**		**Education subset of analysis cohort (n = 11,492)**	
NEONATAL CHARACTERISTICS						
Gestational age, continuous, weeks and days						
Median (range) Mean (SD)	39^{+5} (24^{+6} – 44^{+5}) 39.4 (1.92)		39^{+5} (25^{+5}- 44^{+5}) 39.5 (1.83)		39^{+5} (25^{+5}- 44^{+5}) 39.5 (1.81)	
Birth weight, grams						
Median (range) Mean (SD)	3220 (480 – 5800) 3205.5 (573.0)		3220 (540 – 5700) 3213.9 (559.1)		3220 (660 – 5290) 3208.2 (552.4)	
Missing	334		1		1	
Gestational age, categorised						
	Number	Percentage	Number	Percentage	Number	Percentage
<28 weeks	32	0.2%	21	0.2%	17	0.2%
28 - 31 weeks	118	0.9%	99	0.8%	77	0.7%
32 - 33 weeks	110	0.8%	94	0.7%	78	0.7%
34 - 36 weeks	646	4.8%	606	4.6%	527	4.6%
37 - 38 weeks	3,028	22.4%	2,950	22.4%	2,616	22.8%
39 - 41 weeks	9,407	69.5%	9,222	70.0%	8,026	69.8%
>41 weeks	185	1.4%	180	1.4%	151	1.3%
Missing	332		excluded		excluded	
Child's sex						
Male	6,972	51.6%	6,801	51.6%	5,916	51.5%
Female	6,553	48.5%	6,371	48.4%	5,576	48.5%
Missing	333		nil		nil	
Multiplicity						
Singletons	13,199	97.6%	12,867	97.7%	11,217	97.6%
Twins	318	2.4%	305	2.3%	275	2.4%
Higher order	9	0.1%	excluded		excluded	
Missing	332		nil		nil	
Small for gestational age (SGA)						
Not SGA	11,337	85.9%	11,067	86.0%	9,621	85.8%
SGA	1,857	14.1%	1,795	14.0%	1,591	14.2%
Missing	664		310		280	
Large for gestational age (LGA)						
Not LGA	12,240	92.8%	11,944	92.9%	10,432	93.0%
LGA	954	7.2%	918	7.1%	780	7.0%
Missing	664		310		280	

Note: values are numbers and percentages unless otherwise stated.

Table 28 - Comparison of whole cohort, analysis cohort, and subset with linked education records based on antenatal characteristics

Characteristics	**Whole cohort (n = 13,858)**		**Analysis Cohort (n = 13,172)**		**Education subset of analysis cohort (n = 11,492)**	
ANTENATAL CHARACTERISTICS						
Maternal age, years						
Median (range) Mean (SD)	27 (15-49) 27.5 (5.6)		27 (15-49) 27.5 (5.6)		27 (15-49) 27.5 (5.6)	
Missing	0		0		0	
Parity						
Median (range) Mean (SD)	1 (0-10) 1.16 (1.31)		1 (0-10) 1.16 (1.31)		1 (0-10) 1.19 (1.31)	
missing	829		488		434	
Pre-eclampsia						
	Number	Percentage	Number	Percentage	Number	Percentage
No	12,552	97.3%	12,240	97.3%	10,689	97.4%
Yes	351	2.7%	341	2.7%	287	2.6%
missing	955		591		516	
Gestational diabetes						
No	12,359	92.0%	12,035	92.0%	10,498	91.9%
Yes	1,077	8.0%	1,049	8.0%	921	8.1%
missing	422		88		73	
Type of labour onset						
Spontaneous	9,212	72.1%	9,012	72.4%	7,899	72.6%
Elective caesarean	854	6.7%	827	6.6%	722	6.6%
Induction	2,719	21.3%	2,617	21.0%	2,262	20.8%
Missing	1,073		716		11	
Smoking during pregnancy						
Yes, any	1,885	16.5%	1,782	16.4%	1,564	16.5%
No	9,568	83.5%	9,103	83.6%	7,916	83.5%
Missing	2,405		2,287		2,012	
Alcohol in first 3 months of pregnancy						
Yes, any	1,735	49.7%	1,625	49.6%	1,372	49.8%
No	1,753	50.3%	1,649	50.4%	1,385	50.2%
Missing	10,370		9,898		8,735	
Alcohol since 4th month of pregnancy						
Yes, any	1,306	37.8%	1,211	37.4%	1,019	37.4%
No	2,146	62.2%	2,028	62.6%	1,708	62.6%
Missing	10,406		9,933		8,765	

Table 29 - Comparison of whole cohort, analysis cohort, and subset with linked education records based on socio-demographic characteristics

Characteristics	**Whole cohort (n = 13,858)**		**Analysis Cohort (n = 13,172)**		**Education subset of analysis cohort (n = 11,492)**	
	Number	Percentage	Number	Percentage	Number	Percentage
SOCIO-DEMOGRAPHIC CHARACTERISTICS						
Socio-economic position – five group latent class analysis. Measured during pregnancy						
Least deprived and most educated	2,240	19.6%	2,096	19.3%	1,667	17.6%
Employed not materially deprived	2,273	19.9%	2,160	19.9%	1,863	19.7%
Employed no access to money	1,735	15.2%	1,656	15.3%	1,458	15.4%
Benefits but coping	3,347	29.4%	3,201	29.5%	2,902	30.7%
Most deprived	1,809	15.9%	1,730	16.0%	1,558	16.5%
Missing	2,454		2,329		2,044	
Index of Multiple Deprivation (IMD) 5 groups, at recruitment						
1 (most deprived)	7,615	66.4%	7,272	66.7%	6,403	67.4%
2	2,065	18.0%	1,970	18.1%	1,721	18.1%
3	1,263	11.0%	1,199	11.0%	1,002	10.6%
4	335	2.9%	286	2.6%	227	2.4%
5 (least deprived)	193	1.7%	175	1.6%	144	1.5%
missing	2,387		2,270		1,995	
Receipt of means tested benefits, at recruitment						
Yes	4,692	41.0%	4,496	41.4%	4,077	43.1%
No	6,743	59.0%	6,373	58.6%	5,392	56.9%
Missing	2,423		2,303		2,023	
Mother's highest educational qualification, at recruitment						
<5 GCSE equivalent	2,476	21.9%	2,368	22.0%	2,150	23.0%
5 GCSE equivalent	3,510	31.0%	3,350	31.1%	3,016	32.0%
A-level equivalent	1,657	14.6%	1,590	14.8%	1,375	14.7%
Higher than A-level	2,920	25.8%	2,726	25.3%	2,201	23.5%
Other/foreign unknown	753	6.7%	724	6.7%	626	6.7%
Missing	2,542		2,414		2,124	
Child's Ethnicity						
Asian	7,249	52.7%	6,970	53.2%	6,314	55.0%
Mixed	737	5.4%	704	5.4%	649	5.7%
White	5,300	38.6%	5,001	38.2%	4,198	36.6%
Black	270	2.0%	245	1.9%	169	1.5%
Other	191	1.4%	179	1.4%	156	1.4%
Missing	111		73		6	
Consanguinity (Mother related to father except by marriage)						
Yes	3,442	30.0%	3,328	30.5%	3,098	32.6%
No	8,021	70.0%	7,568	69.5%	6,393	67.4%
Missing	2,395		2,276		2,001	

Table 30 - Comparison of whole cohort, analysis cohort, and subset with linked education records based on postnatal characteristics

Characteristics	**Whole cohort (n = 13,858)**		**Analysis Cohort (n = 13,172)**		**Education subset of analysis cohort (n = 11,492)**	
	Number	Percentage	Number	Percentage	Number	Percentage
POSTNATAL CHARACTERISTICS						
Ever breastfed						
Yes	3,040	77.2%	2,989	77.3%	2,659	76.5%
No	900	22.8%	878	22.7%	817	23.5%
Missing	9,918		9,305		8,016	
Maternal anxiety (measured using Generalized Anxiety Disorder 7-item (GAD-7)), measured in child's primary school years						
Minimal	4,113	74.6%	4,027	74.7%	3,842	74.7%
Mild	829	15.0%	804	14.9%	763	14.8%
Moderate	328	6.0%	319	5.9%	309	6.0%
Severe anxiety	245	4.4%	238	4.4%	227	4.4%
Missing	8,343		7,784		6,351	
Maternal depression (measured using Patient Health Questionnaire-8 (PHQ-8)), measured in child's primary school years						
No significant symptoms	3,862	69.8%	3,786	70.1%	3,614	70.1%
Mild symptoms	1,017	18.4%	983	18.2%	927	18.0%
Moderate symptoms	367	6.6%	363	6.7%	351	6.8%
Moderately severe & severe symptoms	286	5.2%	273	5.1%	264	5.1%
Missing	8,326		7,767		6,336	

4.3. Missing data

The amount of missing data is shown above (Table 27 - Table 30). Alcohol consumption, breastfeeding and both maternal mental health measures were >50% missing in the analysis cohort.

4.3.1 Missingness by ethnicity

Missingness in some variables varied according to ethnicity. Alcohol consumption and receipt of means tested benefits were least missing in White families (42.9% and 14.7% respectively), whereas for Asian women these data were 98.7% and 18.3% missing respectively (Table 31).

Table 31 - Missingness of alcohol consumption and receipt of means tested benefits variable by ethnicity

Ethnicity	**Missing "*mother drank alcohol in the first 3 months of pregnancy*" variable**	**Missing *"means tested benefits received"* variable**	**Total number**
White percentage	2,145 42.9%	736 14.7%	5,001
Mixed percentage	438 62.2%	125 17.8%	704
Asian percentage	6,880 98.7%	1,277 18.3%	6,970
Black percentage	197 80.4%	48 19.6%	245
Other percentage	165 92.2%	47 26.3%	179
Missing Ethnicity percentage	73 100%	70 95.9%	73
Total percentage	9,898 75.1%	2,303 17.5%	13,172

Values are number missing and percentage (of total) missing

4.3.2 Missingness amongst measures of socioeconomic position

All measures of socioeconomic position (SEP) were collected at recruitment, during pregnancy. Measures of SEP tended to be missing in the same children. Patterns of missingness amongst measures of socio-economic position (index of multiple deprivation, maternal education, receipt of means tested benefits and five group LCA) were explored (Table 32).

As described in a previous chapter, whilst means tested benefits (MTB) and mother's highest educational qualification are components in the 5-group latent class analysis (LCA) if these variables are missing it does not necessarily follow that the LCA group will be missing, as missing data was incorporated into the LCA using a full information maximum likelihood approach. However, if data were missing for ethnicity, maternal age, and cohabitation status the participants information would be excluded from the LCA because these variables were used as covariates in the analysis (Fairley, Cabieses, Small et al., 2014).

Table 32 - Patterns of missingness within variables measuring socioeconomic position

Index of multiple deprivation (IMD), maternal education, receipt of means tested benefits (MTB) and 5 group latent class analysis (LCA)

Missingness within variables	Number	Percent
missing for all 4 variables	2,267	17.2%
missing only IMD	3	0.0%
missing MTB, maternal education, LCA	2	0.0%
missing MTB and LCA	1	0.0%
missing only MTB	33	0.3%
missing maternal education and LCA	3	0.0%
missing only maternal education	142	1.1%
missing only LCA	56	0.4%
no missing values (for these 4 variables)	10,665	81.0%

4.3.3 Missing data mechanisms

Potential mechanisms for missing data are discussed in Chapter 5, which presents the results of the statistical modelling.

4.4. Characteristics by exposure (gestational age)

The majority of women in the analysis cohort had at least one ultrasound scan during the course of their pregnancy; 10,232 (out of 13,172 = 77.7%) had a scan between 9-15 weeks; 12,898 (out of 13,172 = 97.9%) had a scan at some point in the pregnancy. The gestational age of the fetus at the first ultrasound scan is shown in the histogram below (Figure 60).

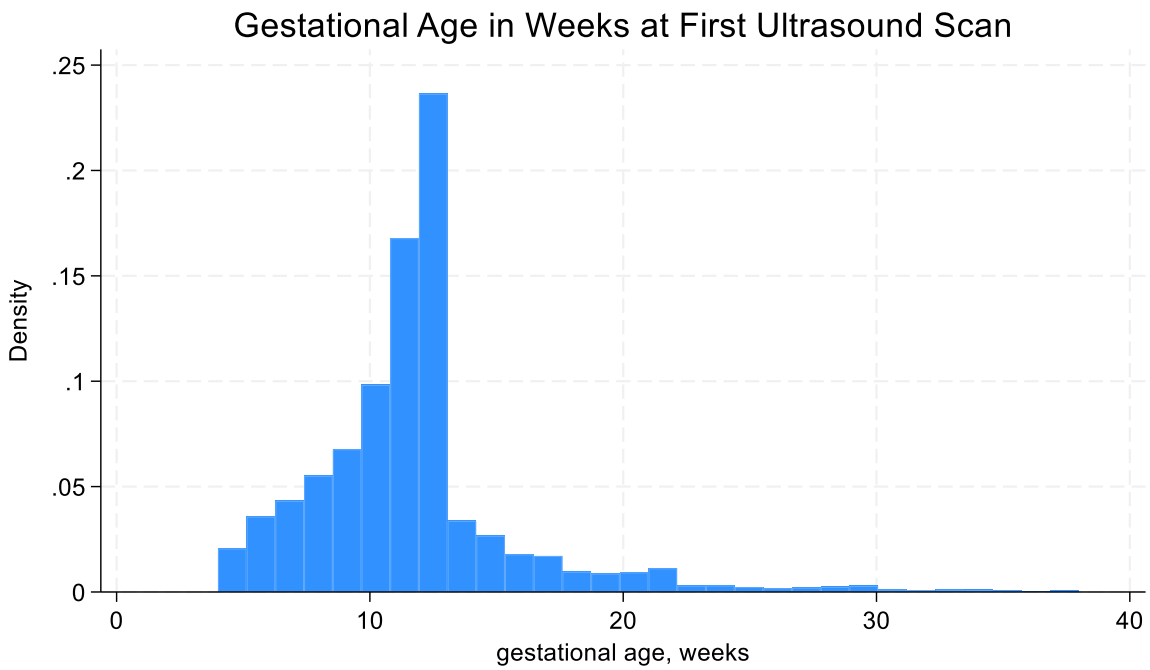


Figure 60 - Gestational age at first ultrasound scan

The distribution of gestational ages at delivery in the analysis cohort is shown in Figure 61 and in Table 67 in appendix 4.1. Given the numbers of children <34 weeks, further results are presented in five categories: <34 weeks ("very preterm" combined with "moderately preterm"), 34-36 weeks ("late preterm"), 37-38 weeks ("early term"), 39-41 weeks ("full term") and >41 weeks ("post term"). There were no babies in the analysis cohort born <25 weeks gestation.

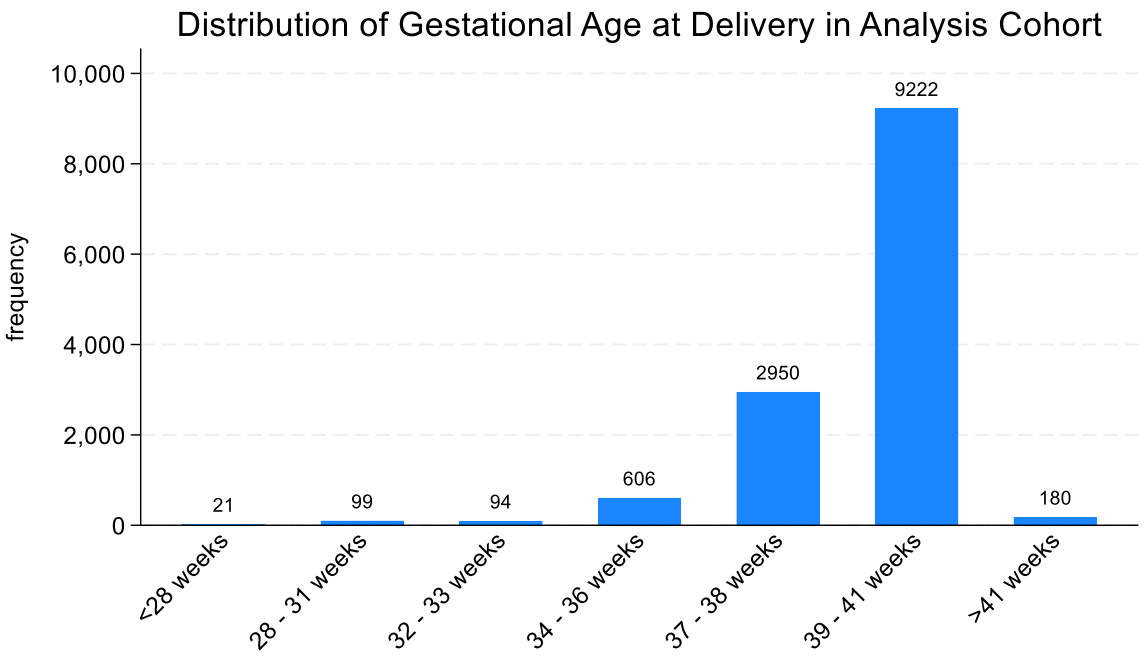


Figure 61 - Distribution of participants across gestational age categories

4.4.1. Neonatal characteristics

The proportion of children in each gestational group is different based on multiplicity and admission to the neonatal unit, also known as the special care baby unit (SCBU), but not based on child's sex (see appendix 4.1). Less than 1% of twins were born at full term, the majority were born early term. Of children admitted to SCBU 33.9% were born at full term, whereas 72.4% of children not admitted to SCBU were full term. However, twenty children <32 weeks were recorded as "not admitted to special care", none of whom died in the neonatal period. Thus, the quality of this variable is questionable, and it will not be used further in this thesis. There is a relationship between SGA and gestational age; there is a higher proportion of children who are SGA who are born post term, and fewer SGA children are born early term. Large for gestational age children are more likely to be born early term.

4.4.2. Antenatal characteristics

The mean maternal age and parity in each gestational age category was similar (see appendix 4). Pre-eclampsia was associated with gestational age, with a higher proportion of babies born to mothers with pre-eclampsia being born before full term: only 40% of women with pre-eclampsia delivered at full term, compared to 71% of women without pre-eclampsia. Gestational diabetes (GDM) was also associated with gestational age; the majority of babies born to mothers with GDM were born early term.

4.4.3. Socio-demographic characteristics

Socio-economic position

Socioeconomic deprivation appears to be associated with gestational age; 6.1% of children in "most deprived" group were born late preterm, compared to 4.6% of the children in the 'least deprived most educated" group.

Ethnicity

The majority of the analysis cohort fall into two ethnic groups: White British (which includes English, Welsh, Scottish, or North Irish) and Pakistani (see Figure 62). As the other ethnic groups are relatively small, for the remaining analyses the five ethnic group variable was used, as per Table 26.

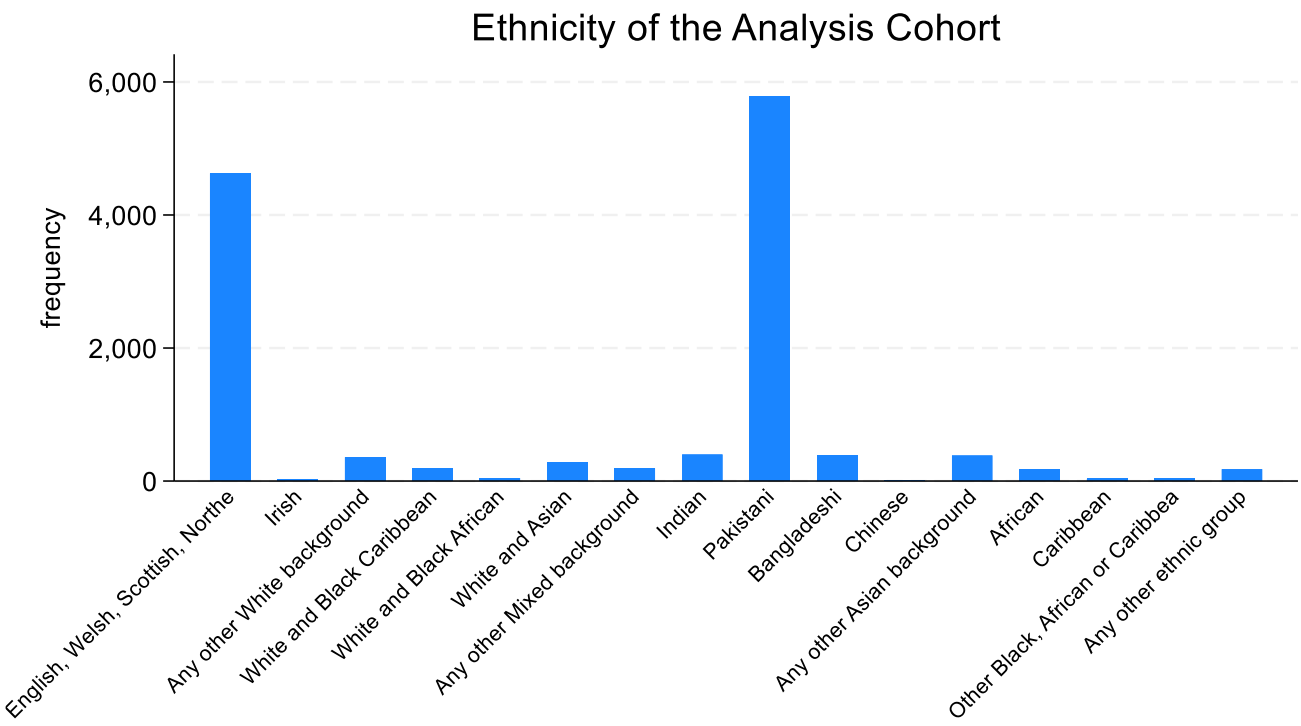


Figure 62 - The distribution of ethnicities within the analysis cohort

Ethnicity is associated with gestational age (Figure 63). In total, 22.4% of babies were born 'early term'. In the Asian group this was 25.0%, and in the White group it was 19.1%, see appendix 4.1., Table 69 and Figure 63.

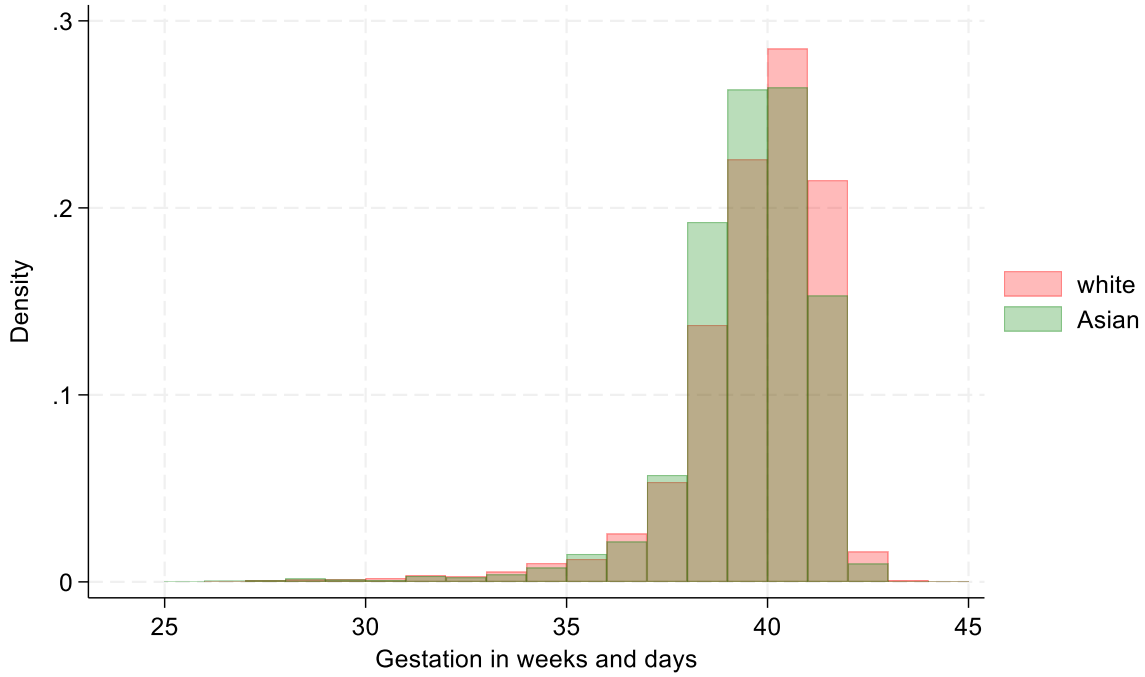


Figure 63 – Histogram showing distribution of gestational age at delivery according to two largest ethnic groups

4.4.4. Postnatal factors

The proportion of babies who had ever been breastfed (Figure 64) was similar in all gestational age groups, except <34 weeks, which had a higher proportion who were ever breastfed.

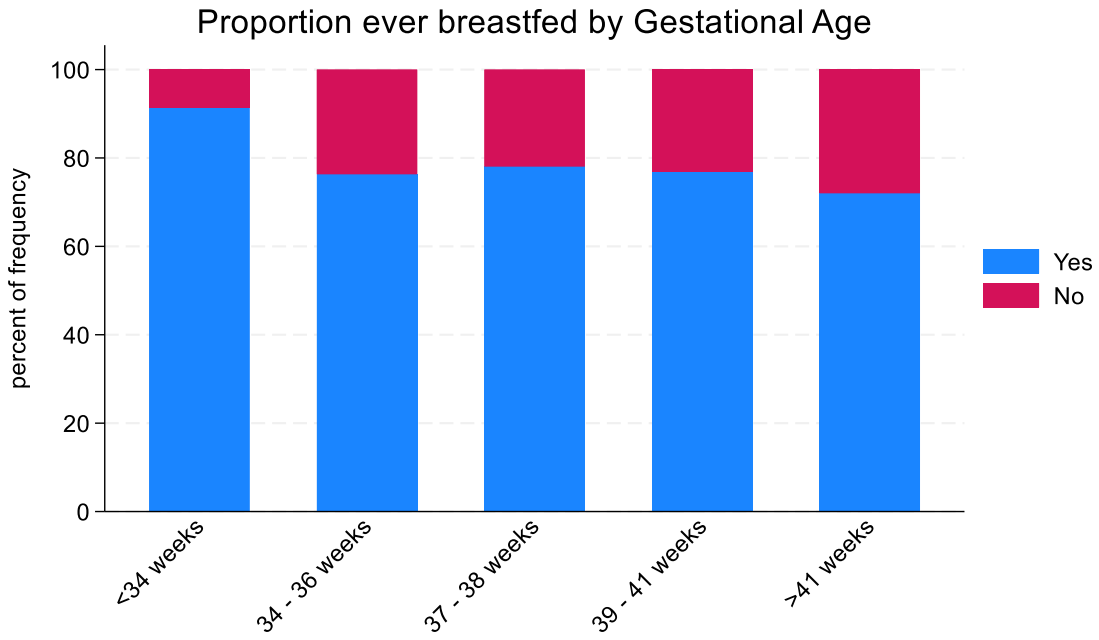


Figure 64 - Bar chart showing proportion of children ever breastfed, by gestational age group. Note that this data was missing for >50% of the children

4.4.5. Deaths and withdrawals

There were 324 children who withdrew or were withdrawn from the study. There was no association between withdrawal and gestational age. In addition, 53 children died, 18.9% of whom were born <37 weeks, whereas only 6.2% of children who did not die were born <37 weeks. These children's data were included up until the point of death/withdrawal.

4.5. Relationship between ethnicity and other covariates

4.5.1 Socio-economic position

Measured by Index of Multiple Deprivation (IMD)

In the analysis cohort 66.7% of the children were in the most deprived fifth, by IMD quintiles, with just 1.6% of participants in the least deprived fifth. Among the children living in the most deprived fifth, 60.9% were Asian, and 30.2% were White. In the least deprived fifth 87.4% were White and 8.6% were Asian (Table 33).

Table 33 - Number and percentage (by column) of children in each Index of Multiple Deprivation group, by ethnicity

	Index of Multiple Deprivation groups					
	1 (most deprived)	**2**	**3**	**4**	**5 (least deprived)**	**total**
White	2,195 30.2%	940 47.7%	749 62.5%	244 85.3%	153 87.4%	4,281 39.3%
Mixed	385 5.3%	116 5.9%	63 5.3%	*	*	579 5.3
Asian	4,426 60.9%	869 44.1%	370 30.9%	30 10.5%	15 8.6%	5,710 52.4%
Black	172 2.4%	17 0.9%	*	*	*	197 1.8
Other	92 1.3%	27 1.4%	*	*	*	132 1.2%
Total	7,270 100%	1,969 100%	1,199 100%	286 100%	175 100%	10,899 100%

** results suppressed to reduce risk of deductive disclosure*

Measured by five group latent class analysis

When the five-group latent class analysis (LCA) is used instead of IMD, the children are distributed more evenly across the five groups (Table 34). There is an association between SEP and ethnicity seen most clearly in the “benefits but coping” group, which has a high proportion (73.8%) of Asian children, and the “employed not materially deprived” group which has a high proportion (65.5%) of White children.

Table 34 - Number and percentage (by column) of children in each socio-economic position latent class by child's ethnicity

Ethnicity	Least deprived, most educated		Employed not materially deprived		Employed no access to money		Benefits but coping		Most deprived		Total	
	n	percentage	n	percentage	n	percentage	n	percentage	n	percentage	n	percentage
White	733	35.0%	1,414	65.5%	667	40.3%	675	21.1%	779	45.0%	4,268	39.4%
Mixed	80	3.8%	125	5.8%	85	5.1%	128	4.0%	141	8.2%	559	5.2%
Asian	1,161	55.4%	588	27.2%	833	50.3%	2,362	73.8%	747	43.2%	5,691	52.5%
Black	60	2.9%	*	*	50	3.0%	*	*	*	*	197	1.8%
Other	62	3.0%	*	*	21	1.3%	*	*	*	*	128	1.2%
Total	2,096	100%	2,160	100%	1,656	100%	3,201	100%	1,730	100%	10,843	100%

** results suppressed to reduce risk of deductive disclosure*

Measured by receipt of means tested benefits

Of the children whose parents were in receipt of means tested benefits during the pregnancy, 58.4% were Asian and 33.7% were White; amongst the children whose parents were not in receipt of means tested benefits the proportions were 48.2% Asian and 43.2% White (Table 35). However, as per section "4.3.1 Missingness by ethnicity", this variable varies with ethnicity.

Table 35 - Number and percentage (by column) of children whose parents were in receipt of means tested benefits, by ethnicity

Ethnicity	**In receipt of means tested benefits**	**Not in receipt of means tested benefits**	**Total**
White	1,513 33.7%	2,752 43.2%	4,265 39.3%
Mixed	273.0 6.1%	306.0 4.8%	579.0 5.3%
Asian	2,625 58.4%	3,068 48.2%	5,693 52.4%
Black	47 1.1%	150 2.4%	197 1.8%
Other	38 0.9%	94 1.5%	132 1.2%
Total	4,496 100%	6,370 100%	10,866 100%

4.5.2. Consanguinity

Consanguinity is associated with ethnicity; 57.4% of Asian women were related to the baby's father other than by marriage, compared to 0.5% of White women (Table 36).

Table 36 - Consanguinity by ethnicity

Ethnicity	mother related to baby's father other than by marriage		Total
	No	Yes	
White Percentage	4260 99.5%	20 0.5%	4,280 100%
Mixed Percentage	562 97.1%	17 2.9%	579 100%
Asian Percentage	2433 42.7%	3272 57.4%	5,705 100%
Black Percentage	*	*	197 100%
Other Percentage	115 87.1%	17 12.9%	132 100%
Total Percentage	7565 69.5%	3328 30.6%	10,893 100%

*Percentages by row. *data suppressed when <10 participants*

4.5.3. Antenatal characteristics

Asian babies were more likely than White babies to be small for gestational age; 17.9% of Asian babies were SGA compared to 9.3% of White babies (Table 37).

Table 37 - Small for gestational age (SGA) by ethnicity

Ethnicity	Not SGA	SGA	Total
White	4,435 90.7%	453 9.3%	4,888 100%
Mixed	611 89.2%	74 10.8%	685 100%
Asian	5,587 82.1%	1,218 17.9%	6,805 100%
Black	217 91.2%	21 8.8%	238 100%
Other	158 90.3%	17 9.7%	175 100%
Total	11,008 86.1%	1,783 13.9%	12,791 100%

Gestational diabetes is more than twice as common in Asian women (10.7%) compared to White women (4.8%) (Table 38).

Table 38 - Gestational Diabetes (GDM) by ethnicity

Ethnicity	Not GDM	GDM	Total
White	4,725 95.2%	237 4.8%	4,962 100%
Mixed	664 96.1%	27 3.9%	691 100%
Asian	6,192 89.2%	747 10.8%	6,939 100%
Black	232 94.7%	13 5.3%	245 100%
Other	159 88.8%	20 11.2%	179 100%
Total	11,972 92.0%	1,044 8.0%	13,016 100%

Pre-eclampsia did not appear to be associated with ethnicity (Table 39).

Table 39 - Pre-eclampsia by ethnicity

Ethnicity	No pre-eclampsia	pre-eclampsia	Total
White	4,633 97.1%	138 2.9%	4,771 100%
Mixed	658 98.1%	13 1.9%	671 100%
Asian	6,494 97.4%	175 2.6%	6,669 100%
Black	*	*	234 100%
Other	*	*	171 100%
Total	12,179 97.3%	337 2.7%	12,516 100%

** results suppressed to reduce risk of deductive disclosure*

Asian women appeared to be more parous than other ethnicities, although the median parity was the same (1) for all ethnicities (Table 40).

Table 40 - Summary statistics for maternal parity by ethnicity

Ethnicity	Mean	Standard deviation	Median	Range
White	0.84	1.09	1	0-10
Mixed	0.99	1.23	1	0-8
Asian	1.42	1.41	1	0-10
Black	0.93	1.08	1	0-6
Other	1.01	1.17	1	0-5

Mothers of children in the Black and 'Other' groups have a higher mean age at delivery (Table 41).

Table 41 - Summary statistics for maternal age at delivery (in years) by ethnicity

Ethnicity	Mean	Standard deviation	Median	Range
White	26.9	6.00	26	15-46
Mixed	26.3	6.06	26	15-45
Asian	28.0	5.15	28	16-49
Black	29.2	5.48	29	18-45
Other	29.8	5.67	31	15-42

4.6. Participant age and academic year at data extract

At the point of the primary care data extract, the children were aged 11-15 years (Figure 65).

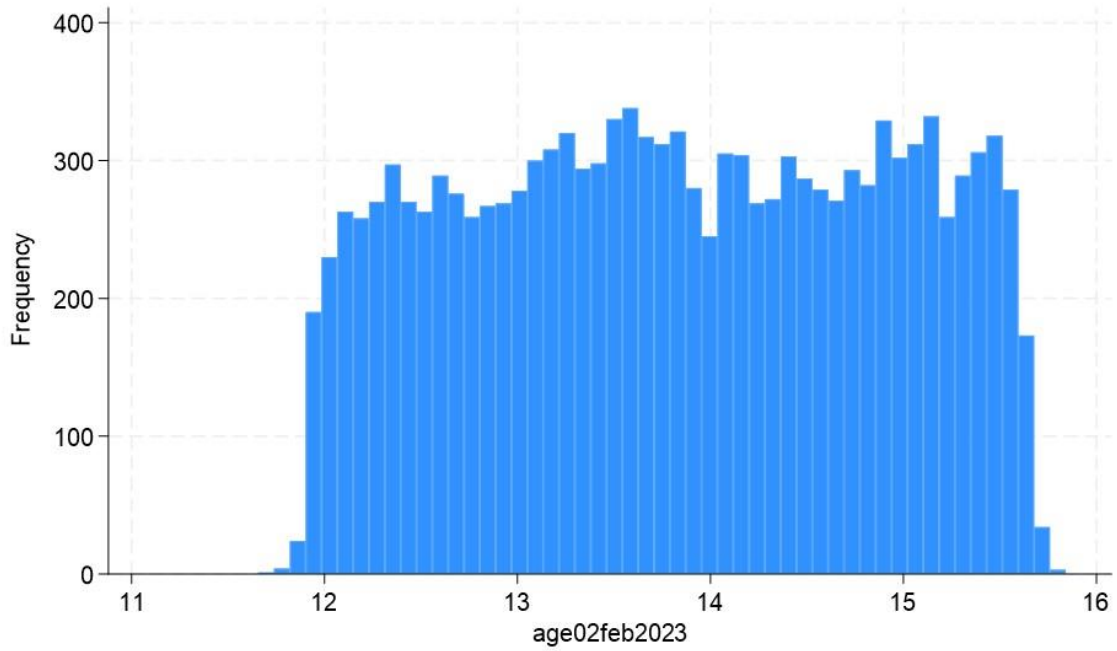


Figure 65 - Age of participants at data extract

For the calculation of cumulative incidence, children were included from birth until their approximated 12th birthday. There were 219 children (out of a total of 13,172) who were not yet 12 at the point of data extract. However, 35 (15.9%) of these had already received a primary or secondary care diagnosis, which is higher than the overall cumulative incidence of any developmental disorder (see section 4.7. Cumulative incidence of developmental disorders) so it seemed unlikely there would be substantially more incident cases in the remaining months before those children's 12th birthdays. Therefore, the child's 12th birthday was chosen as the cut off for cumulative incidence, to minimise loss of data. The key outcome "primary or secondary care diagnosis" was changed from "1" (a diagnosis), to "0" (no diagnosis) if the age at the first code was >143 months.

Education Records

For the subgroup of children with linked education records data was available from Reception up to Year 10 for the oldest participants. The proportion of children without data increased from year 7 onwards (Table 42 and Figure 66) as the participants had not reached the older year groups yet, so cumulative incidence up to (and including) year 7 was calculated. Children in school year 7 are aged between 11-12 years therefore this was consistent with the decision to use the approximated 12th birthday as the cut point for cumulative incidence.

Table 42 - Number and percentage of children with missing Special Educational Need and Disability data, and total number of records per academic year

	Number missing	% missing	Total with records (including missing data)
Reception	5,612	49	11,492
Year 1	306	3	11,492
Year 2	148	1	11,492
Year 3	204	2	11,492
Year 4	222	2	11,492
Year 5	224	2	11,492
Year 6	225	2	11,492
Year 7	229	2	11,492
Year 8	204	2	9,905
Year 9	100	1	6,921
Year 10	38	1	3,858

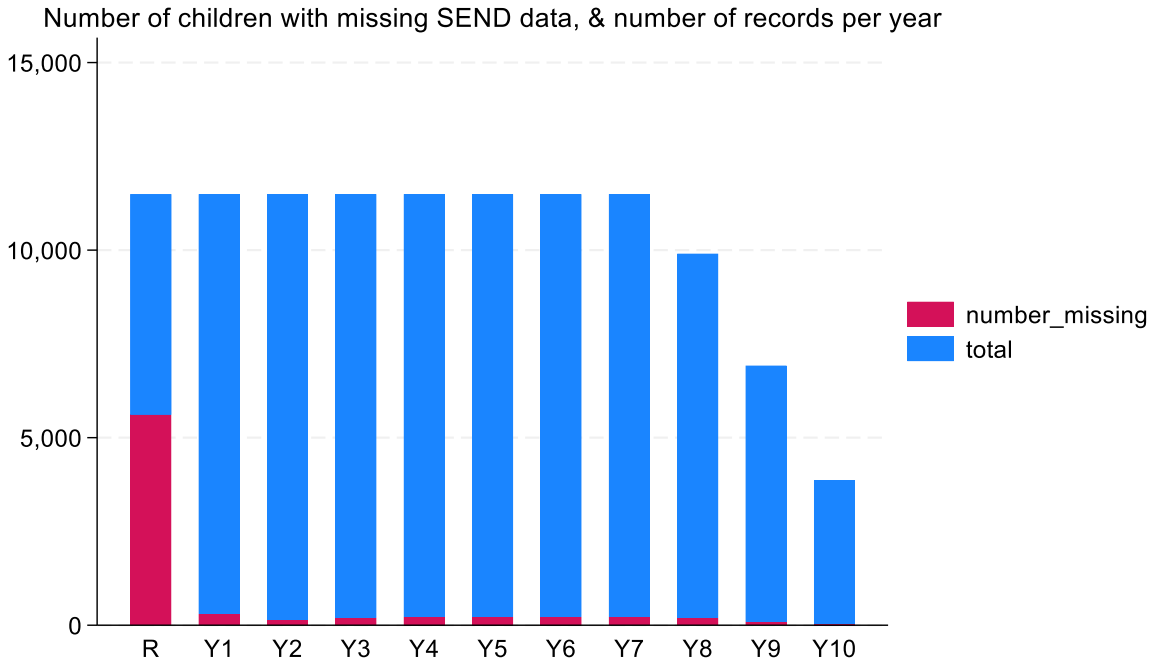


Figure 66 - Number of children with missing Special Educational Need and Disability data, and total number of records per academic year

4.7. Cumulative incidence of developmental disorders

4.7.1. Medical records

Using a cut off of the participants' 12th birthdays there were 1,497 incident diagnoses of a developmental disorder, out of the analysis cohort of 13,172. As per the methods, for the 'overall' cumulative incidence of any developmental disorder presented here a child can only be counted once. The cumulative incidence is therefore 11.4% (95% CI: 10.8 to 11.9%). As always with cumulative incidence, this does not take into account any deaths or withdrawals. There were 1,355 incident diagnoses in the primary care records, therefore the cumulative incidence from primary care was 10.3% (95% CI: 9.8 to 10.8%). There were 524 incident diagnoses in the secondary care records, therefore the cumulative incidence from secondary care was 4.0% (95% CI: 3.7 to 4.3%).

Exploratory analysis

An exploratory analysis removing all diagnostic codes which occurred before the child's 2nd birthday, in order to be consistent with the systematic review, showed similar results: overall cumulative incidence is 10.6% (95% CI: 10.1 to 11.2). This approach made minimal difference, probably because many of the children who had a code in their medical notes before age 2 on went on to have another code later and so still counted as cases. This blanket approach of a 2 year cut off will not be explored further.

4.7.1.1. Most common incident primary care diagnoses

The twenty most common incident primary care codes are shown in Table 43.

Table 43 - Twenty most common incident primary care codes occurring before participants' 12th birthday

Clinical Term version 3 (CTV3)	**frequency**
Developmental language delay	174
Speech delay	145
Learning difficulties	118
Developmental delay	112
Autistic spectrum disorder	86
Sleep apnoea	74
Obstructive sleep apnoea	68
Speech and language disorder	45
Behavioural, emotional and social difficulties	43
Attention deficit hyperactivity disorder	32
Impaired vision	32
Expressive language delay	24
Pica of infancy and childhood	24
Delayed milestone	20
Sensorineural hearing loss	20
Global developmental delay	19
[V]Other behavioural problems	15
Disorder of speech and language development	13
Sensorineural hearing loss, bilateral	13
Childhood autism	12

4.7.1.2. Most common secondary care diagnoses

The ten most common incident codes from secondary care are shown below in Table 44; only the ten most common are shown, as the remaining codes appeared <10 times.

Table 44 - Ten most common incident secondary care codes occurring before participants' 12th birthday

ICD-10 term	frequency
Sleep apnoea	134
Childhood autism	78
Lack of expected normal physiologic development	64
Developmental disorder of speech & language - unspecified	44
Unspecified mental retardation; Without mention of impairment of behaviour	19
Developmental disorder of scholastic skills - unspecified	18
Developmental disorder of speech and language, unspecified	16
Unspecified disorder of psychological development	16
Feeding difficulties & mismanagement	15
Mixed specific developmental disorders	11

4.7.2. Education records

Up to and including academic year 7 there were 3,086 incident records of SEND in the education records, out of a total of 11,368. The cumulative incidence of SEND is therefore 27.1% (95% CI: 26.3 to 28.0). This does not take into account any deaths or withdrawals.

Up to and including academic year 7 there were 414 incident cases of EHCP (or statements) in the education records. The cumulative incidence of EHCPs (previously statements) was therefore 3.6% (95% CI: 3.3 to 4.0%).

4.7.3. Intersection between developmental disorder in primary and secondary health care records and SEND in education records

The intersection between developmental disorder codes in primary and secondary health care records and any SEND in education records for children with linked education data is shown in Table 45 and Figure 67.

Table 45 - Intersection between primary healthcare codes, secondary healthcare codes, and SEND in educational records

n	%	Outcome
251	2.2%	primary care code only
66	0.6%	secondary care code only
2,061	18.1%	SEND in education records only
61	0.5%	primary care code and secondary care code
665	5.8%	primary care code and SEND in education records
62	0.5%	secondary care code and SEND in education records
298	2.6%	primary care code and secondary care code and SEND
7,904	69.5%	none

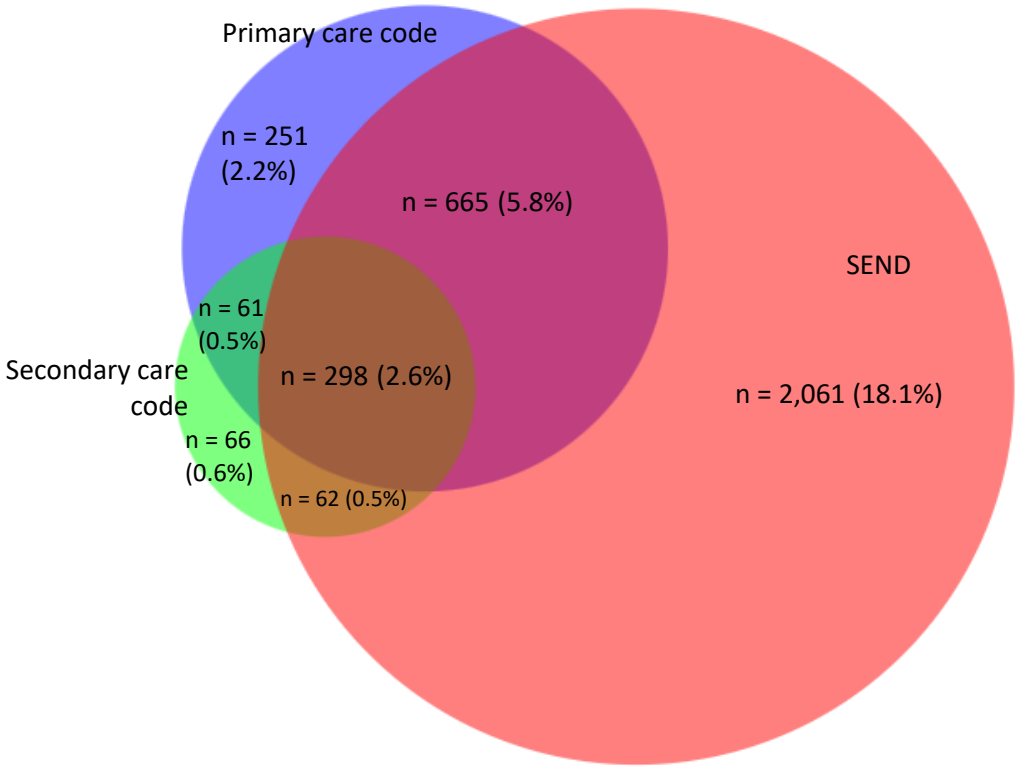


Figure 67 - Venn diagram to show the proportions of children with a developmental disorder in their primary care (blue), secondary care records (green), or any Special Educational Needs and Disabilities (SEND)(orange) in their educational records, and how these intersect

The overlap between developmental disorder in primary and secondary health care records and an EHCP or statement for children with linked education data is shown in Table 46 and Figure 68.

Table 46 - Intersection between primary healthcare codes, secondary healthcare codes, and EHCP (or statements) in educational records

n	%	Outcome
714	6.3%	primary care code only
125	1.1%	secondary care code only
22	0.2%	EHCP (or statement) in education records only
172	1.5%	primary care code and secondary care code
202	1.8%	primary care code and EHCP (or statement) in education records
3	0.0%	secondary care code and EHCP (or statement) in education records
187	1.6%	primary care code and secondary care code and EHCP
9,943	87.5%	none

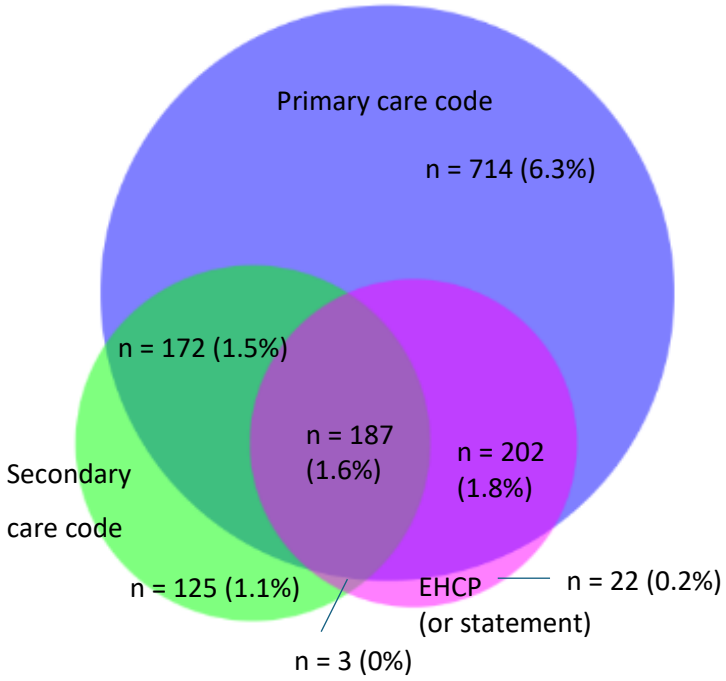


Figure 68 - Venn diagram to show the proportions of children with a developmental disorder in their primary care records (blue), secondary care records (green), or an educational health and care plan (EHCP) or statement in their educational records (pink), and how these intersect

There were only 22 children with an EHCP (or statement) who did not also have a code corresponding to a developmental disorder in either their primary or secondary healthcare records. This could suggest that the case ascertainment strategy has been largely successful; if there had been a large number of children with EHCPs without a diagnosis that the coding framework had detected it might suggest the framework was ineffective. Given that there are so few additional children added to the total number of cases who would not already be cases due to presence of a code in their healthcare records, it was decided not to use the "ever any EHCP" variable in any further analyses.

4.7.4. Age at first code

The median age at first code relating to any developmental disorder in primary care is 4.3 years (range 0-11 years). The median age at first code in secondary care is 4.9 years (SD: 3.2, range 0-11 years). The most common academic year that a child first had SEND recorded in their education records was year 1.

4.8. Incidence rate of developmental disorder

4.8.1. Medical records

There was a total of 1,640 incident codes corresponding to the signs, symptoms or diagnosis of any developmental disorder (as per NICE) within the medical records, and 164,823.2 person years. The incidence rate was 10.0 (95% CI 9.5 to 10.4) per 1,000 person years. The years exposed dichotomised by absence/presence of the outcome are shown in Figure 69.

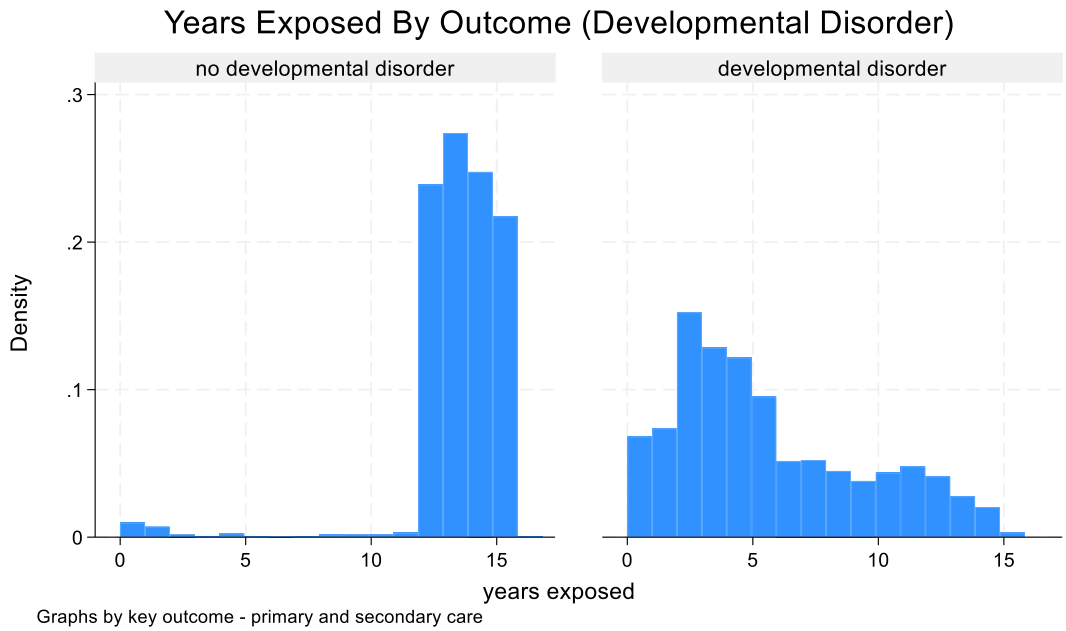


Figure 69 - Histogram of years exposed in medical records

4.8.2. Education records

There was a total of 3,188 incident records of SEND in education records and 138,778.3 person years. The incidence rate was 23.0 (95% CI 22.2 to 23.8) per 1,000 person years. The years exposed dichotomised by absence/presence of the outcome are shown in Figure 70.

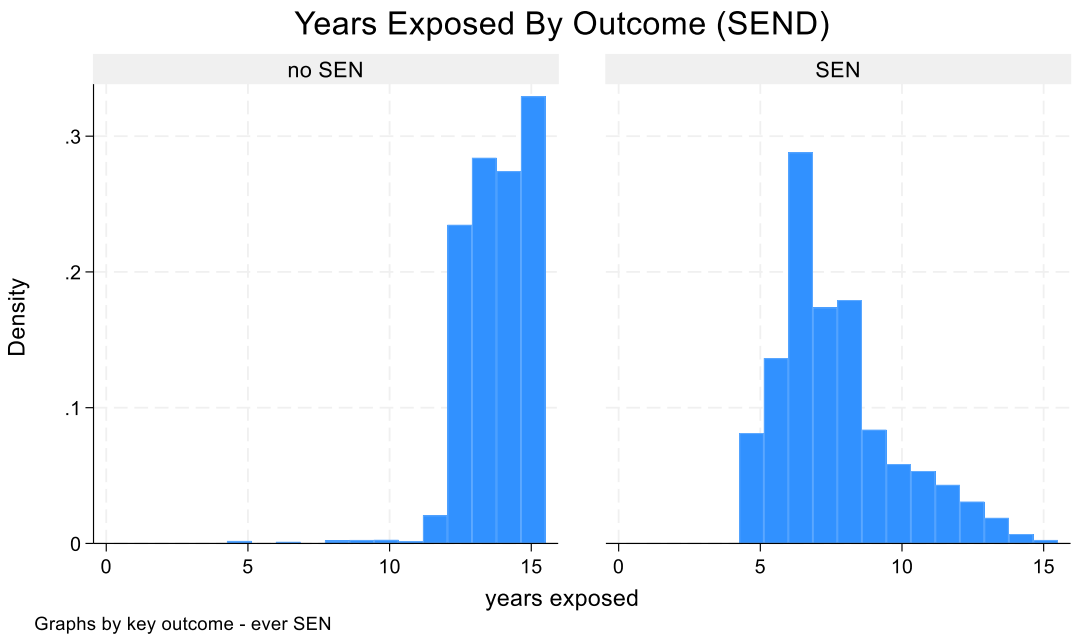


Figure 70 - Histogram of years exposed in education records

4.9. Individual developmental disorders

The analyses presented in this section (4.9) allow for co-occurrence of developmental disorders. For example, if a child had codes relating to both cerebral palsy and visual impairment, they would be counted as a case for *both* disorders. The child's age at which the first code corresponding to each individual developmental disorder appeared in the records was used to calculate age at first clinical code and incidence rate of individual disorders, as presented in Tables 47 and 48, respectively.

This differs from the "overall" incidence rate and cumulative incidence as presented above in sections 4.7 and 4.8, where the first code corresponding to *any* developmental disorder was counted as the singular incident diagnosis.

As in all the analyses in this thesis, if a child had multiple codes all corresponding to the same disorder (for example, both "Other cerebral palsy" and "Cerebral Palsy, unspecified") only the first code (chronologically) was counted. Thus, a child was only counted once as an incident case for each individual disorder but could be recorded as having multiple disorders (if applicable) in the analysis presented below.

4.9.1. Age at first clinical code

The median (and mean) age at the point the first code appeared in their records varied substantially between disorders, from as young as 16 months up to 134 months (11 years) (see Table 47 and Figure 71).

Table 47 - Age in months at first appearance of code in medical record, sorted by youngest to oldest mean age at first code

Developmental disorder	mean	standard deviation	median	range
Feeding problems	26.7	32.5	16	6-167
Cerebral palsy	38.3	32.8	31	7-132
Developmental delay	38.9	31.9	32	2-172
Speech, language, and communication problems	50.2	25.6	45	14-171
Hearing impairment	52.0	46.4	47	0-171
Motor function problems	53.4	40.3	40	3-154
Unclassified / general	54.0	36.8	46	6-171
Visual impairment	65.3	41.3	63	1-172
Sleep apnoea	68.7	31.9	65	0-163
Education problems	90.8	32.5	89	17-157
Learning disability (intellectual disability)	106.2	38.1	106	9-184
Autism spectrum disorder (ASD)	108.5	41.8	115	27-182
Social, emotional, and behavioural problems	108.8	43.7	116	3-180
Attention deficit hyperactivity disorder (ADHD)	126.4	32.8	134	40-181

In order not to lose information (especially important here as some of the individual disorders are rare) incidence rate (as opposed to cumulative incidence) has been used as the measure of disease frequency for the following section (4.9).

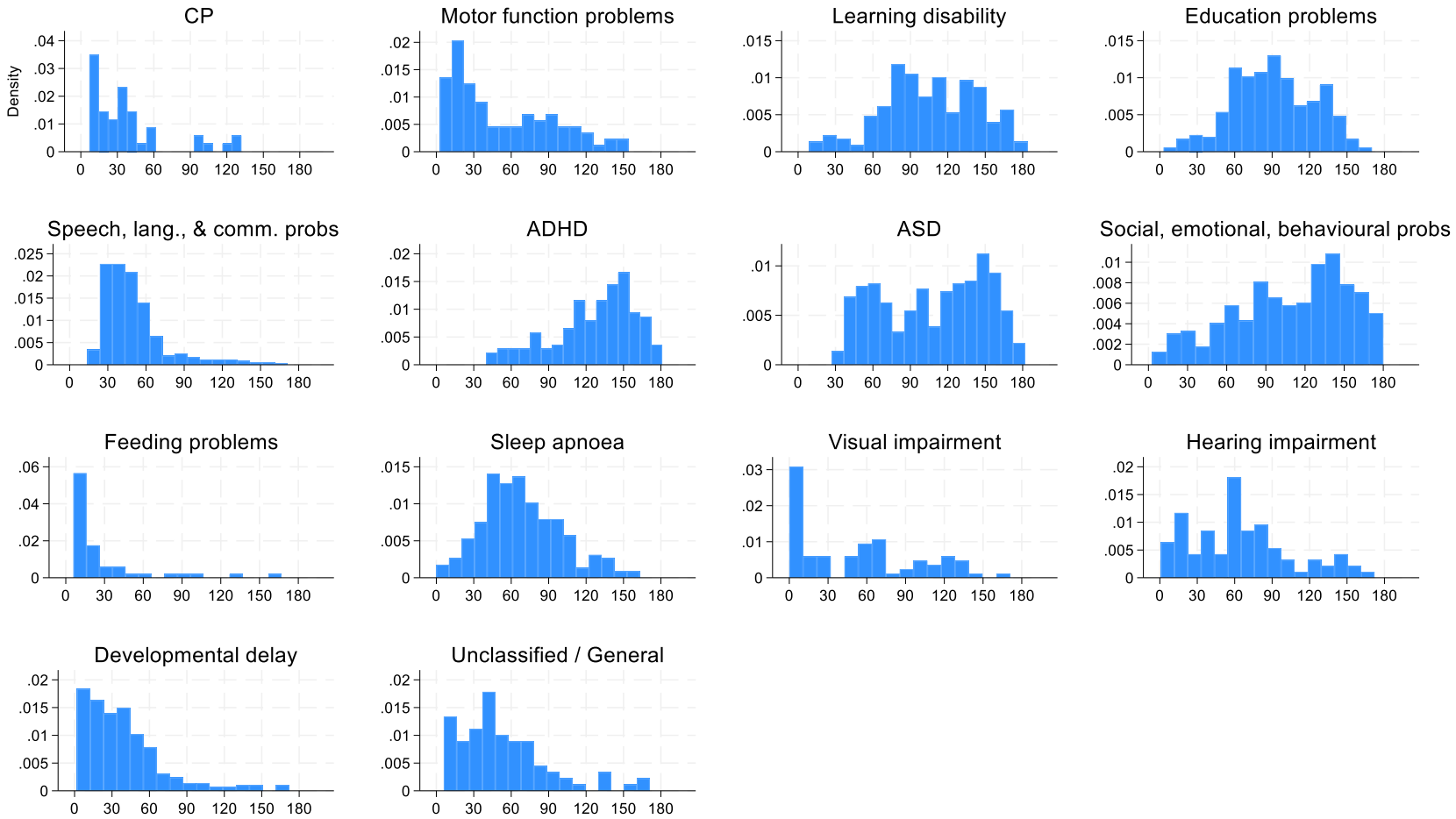


Figure 71 - Histograms showing children's age (months) when the first code corresponding to a developmental disorder appeared in their medical records.

CP: cerebral palsy, ADHD: Attention Deficit Hyperactivity Disorder, ASD: Autism Spectrum Disorder. Note if a child had multiple disorders, they would appear in multiple graphs, but if they had multiple codes all corresponding to the same disorder, they appear only once.

4.9.2. Incidence rate of each disorder

The incidence rate per 1,000 person years of each disorder is shown below, in order of the highest rate to the lowest (Table 48) and in Figure 72.

Table 48 - Incidence rate of each disorder, sorted by incidence rate

Developmental disorder	person-years	Cases	Incidence rate (/1,000 person years)	95% confidence interval	
Speech, language, and communication disorders	172,328.3	606	3.52	3.25	3.81
Autism spectrum disorders	176,407.5	377	2.14	1.93	2.36
Social, emotional, and behavioural problems	176,426.5	359	2.03	1.83	2.26
Education problems	176,004.7	340	1.93	1.74	2.15
Developmental delay	175,405.0	277	1.58	1.40	1.78
Sleep apnoea	176,433.6	222	1.26	1.1	1.44
Learning difficulties	177,095.3	209	1.18	1.03	1.35
Attention, impulsivity, and hyperactivity including ADHD	177,638.9	157	0.88	0.76	1.03
Motor function problems	177,308.2	94	0.53	0.43	0.65
Visual impairment	177,457.7	88	0.50	0.4	0.61
General developmental disorder	177,393.0	87	0.49	0.40	0.61
Hearing impairment	177,434.7	76	0.43	0.34	0.54
Feeding problems	177,641.3	51	0.29	0.22	0.38
Cerebral palsy	177,739.8	44	0.25	0.18	0.33

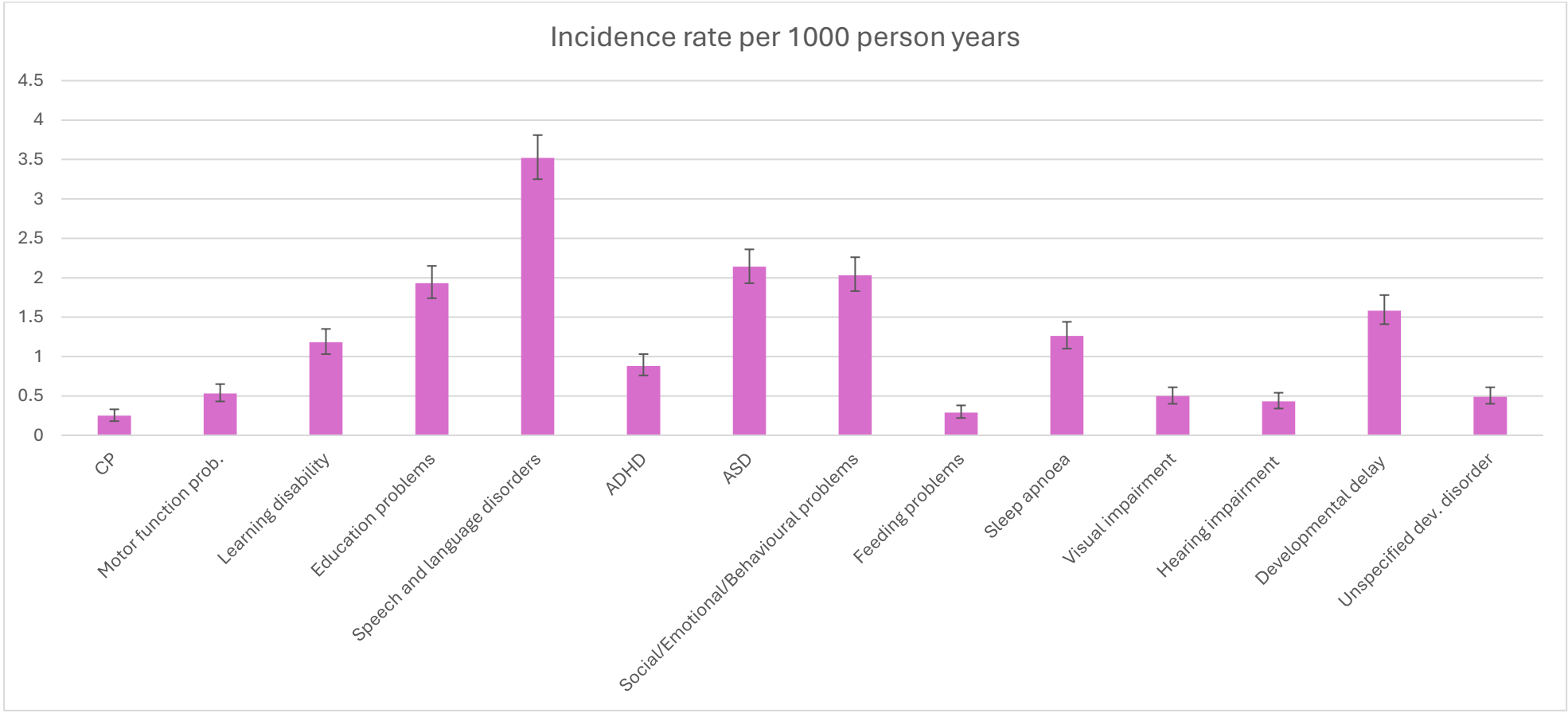


Figure 72 - Bar chart showing incidence rate of each disorder, per 1,000 person years, with 95% confidence intervals.

Shown in order of appearance in the NICE guideline. CP: cerebral palsy, ADHD: Attention deficit hyperactivity disorder, ASD: Autism spectrum disorder

4.9.3. Incidence rate of individual developmental disorders by ethnicity

The incidence rate per 1,000 person years of each developmental disorder split by the two largest ethnic groups is shown below (Table 49 and Figure 73). White children had a higher incidence rate (/1,000 person years) of ASD (3.4, 95% CI 3.0 to 3.9 vs. 1.2, 95% CI 1.0 to 1.4), ADHD (1.7, 95% CI 1.4 to 2.0 vs. 0.3, 95% CI 0.2 to 0.4), and social, emotional, and behavioural problems (1.32, 95% CI 1.11 to 1.58 vs. 3.01, 95% CI 2.62 to 3.46) compared to Asian children, respectively. Asian children had a higher incidence of learning disabilities (1.5, 95% CI 1.3 to 1.8 vs. 0.7 95% CI 0.6-1.0) and hearing impairments (0.58, 95% CI 0.44 to 0.75 vs. 0.25, 95% CI 0.16 to 0.40) compared to White children.

Table 49 - Incidence rate per 1,000 person years of developmental disorders by ethnicity, split by two largest ethnic groups

	Asian children			**White Children**		
Developmental disorder	**Rate**	**lower 95%CI**	**upper 95% CI**	**Rate**	**lower 95%CI**	**upper 95% CI**
Cerebral palsy	0.32	0.22	0.46	0.18	0.10	0.31
Motor function problems	0.55	0.41	0.72	0.56	0.41	0.77
Learning disability (intellectual disability)	1.53	1.30	1.81	0.72	0.55	0.96
Education problems	2.19	1.91	2.52	1.64	1.36	1.97
Speech, language, communication disorder	3.42	3.06	3.82	3.79	3.34	4.29
Attention deficit hyperactivity disorder	0.28	0.19	0.41	1.66	1.38	2.00
Autism Spectrum Disorder (ASD)	1.18	0.98	1.42	3.39	2.97	3.86
Feeding problems	0.38	0.28	0.53	0.16	0.09	0.29
Sleep apnoea	1.25	1.04	1.50	1.32	1.08	1.63
Social/Emotional/ Behavioural problems	1.32	1.11	1.58	3.01	2.62	3.46
Hearing impairment	0.58	0.44	0.75	0.25	0.16	0.40
Visual impairment	0.60	0.46	0.78	0.38	0.26	0.56
Developmental delay	1.83	1.58	2.13	1.37	1.12	1.68
Unspecified developmental disorder	0.57	0.43	0.74	0.37	0.25	0.55

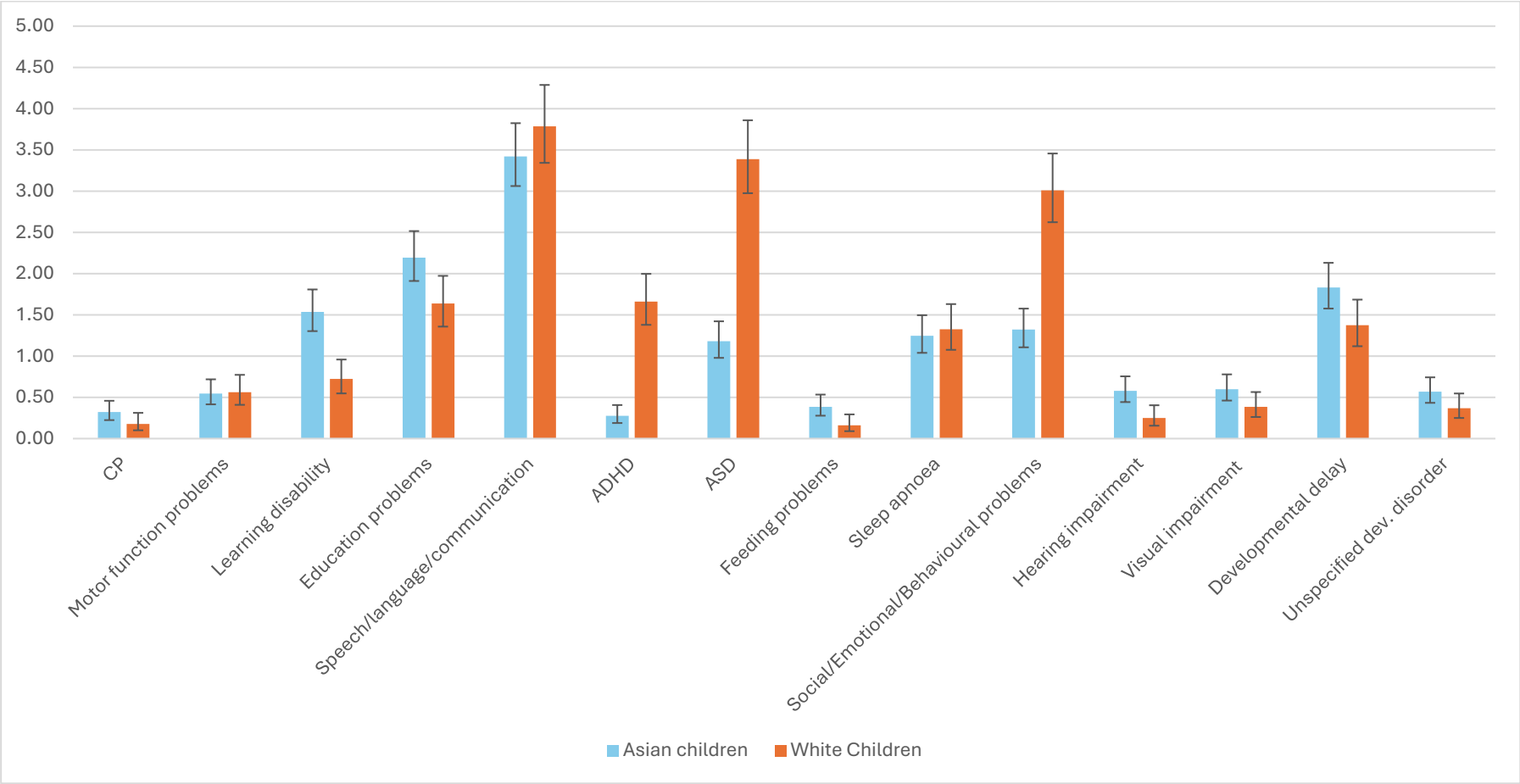


Figure 73 - Bar chart showing incidence rate of each group of disorders, per 1,000 person years, with 95% confidence intervals, split by largest ethnic groups.

CP: cerebral palsy, ADHD: Attention deficit hyperactivity disorder, ASD: Autism Spectrum Disorder

4.10. Prevalence of Special Educational Needs and Disabilities (SEND)

The prevalence of SEND in education records varied according to academic year. The prevalence of SEND peaks in year 6, at 20.5% (95% confidence intervals 19.8 to 21.3%) (Table 50 and Figure 74).

Table 50 - Prevalence of any Special Educational Needs and Disabilities by academic year

	Number with any SEND	Number without SEND	Total	prevalence of 'any SEND'	95% Confidence Intervals	
Reception	332	5,548	5,880	5.7%	5.1%	6.3%
Y1	1,083	10,103	11,186	9.7%	9.1%	10.2%
Y2	1,620	9,724	11,344	14.3%	13.6%	14.9%
Y3	2,032	9,256	11,288	18.0%	17.3%	18.7%
Y4	2,162	9,108	11,270	19.2%	18.5%	19.9%
Y5	2,265	9,003	11,268	20.1%	19.4%	20.9%
Y6	2,310	8,957	11,267	20.5%	19.8%	21.3%
Y7	2,306	8,957	11,263	20.5%	19.7%	21.2%
Y8	1,928	7,773	9,701	19.9%	19.1%	20.7%
Y9	1,324	5,497	6,821	19.4%	18.5%	20.4%
Y10	728	3,092	3,820	19.1%	17.8%	20.3%

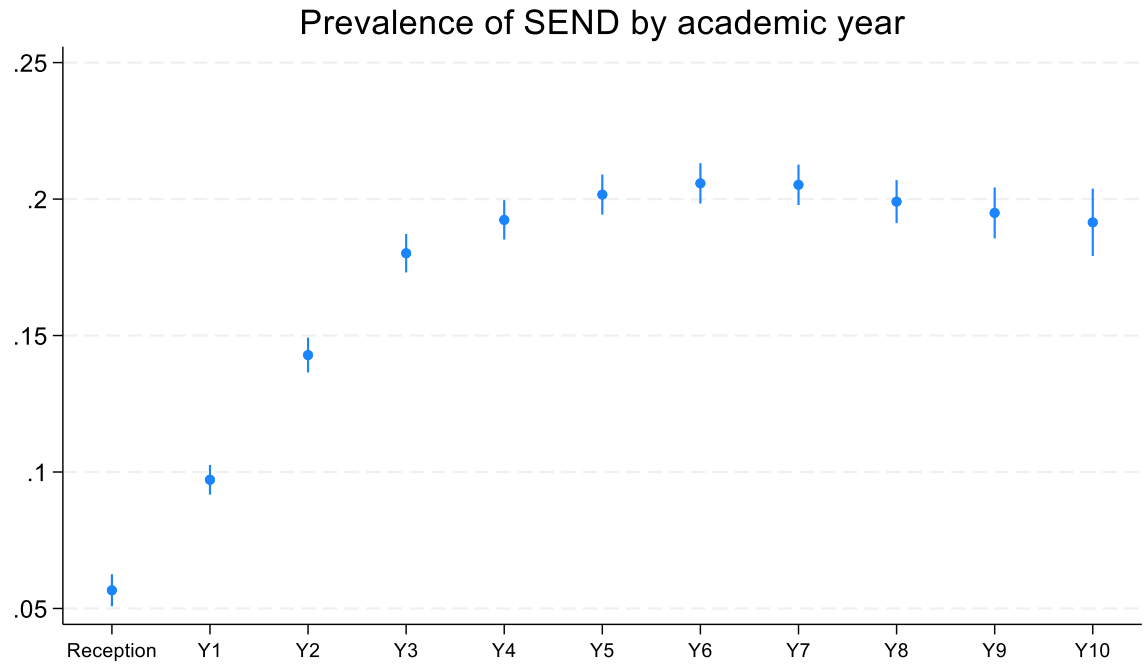


Figure 74 - Prevalence of any type of Special Educational Needs and Disabilities by academic year

Vertical lines = 95% confidence intervals

4.11. Sensitivity analysis - Cumulative incidence of developmental disorders using restricted case ascertainment strategy

Excluding codes relating to sleep apnoea results in a cumulative incidence of any developmental disorder of 10.1% (9.54 to 10.6%). When restricting further to only diagnostic codes corresponding to DSM-IV or ICD-10 developmental disorders (i.e. excluding codes related to developmental 'problems', signs, or symptoms) the cumulative incidence was 8.9% (8.4 to 9.4%), see Table 51. The most common codes are different when this restricted case ascertainment strategy is used (compare Table 52 and Table 53 with Table 43 and Table 44).

The fully restricted case ascertainment strategy is used again, later in section 5.4.1.5, where the relationship between gestational age and developmental disorders is modelled using logistic regression, and the results from the unrestricted and restricted case ascertainment strategy are compared.

Table 51 - Cumulative incidence of developmental disorder using unrestricted and restricted case ascertainment strategies

	Number of incident cases	**Cumulative incidence (95% confidence intervals)**
Unrestricted case ascertainment strategy (main results)		
Primary care	1,355	10.3% (9.8 to 10.8%)
Secondary care	524	4.0% (3.7 to 4.3%)
Combined	1,497	**11.4%** (10.8 to 11.9%)
Partially restricted case ascertainment strategy – excluding sleep apnoea codes		
Primary care	1,224	9.3% (8.8 to 9.8%)
Secondary care	399	3.0% (2.7 to 3.3%)
Combined	1,330	**10.1%** (9.5 to 10.6%)
Fully restricted case ascertainment strategy – excluding sleep apnoea codes and codes relating to developmental 'problems', signs, or symptoms		
Primary care	1,110	8.4% (8.0 to 8.9%)
Secondary care	321	2.4% (2.2 to 2.7%)
Combined	1,117	**8.9%** (8.4 to 9.4%)

Table 52 – Ten most common incident primary care codes occurring before participants' 12th birthday when using fully restricted case ascertainment strategy

Clinical Term Version 3 (CTV3)	**frequency**
Developmental language delay	182
Speech delay	157
Autistic spectrum disorder	148
Learning difficulties	147
Developmental delay	123
Attention deficit hyperactivity disorder	77
Speech and language disorder	50
Impaired vision	36
Expressive language delay	26
Pica of infancy and childhood	24

Table 53 – Most common incident secondary care codes occurring before participants' 12th birthday when using fully restricted case ascertainment strategy

ICD-10 term	**frequency**
Childhood autism	87
Developmental disorder of speech & language - unspecified	47
Developmental disorder of scholastic skills - unspecified	26
Unspecified mental retardation; Without mention of impairment of behaviour	22
Unspecified disorder of psychological development	20
Developmental disorder of speech and language, unspecified	18
Mixed specific developmental disorders	18
Disturbance of activity and attention	12
Cerebral palsy, unspecified	11

Only nine terms included as the remaining codes appeared <10 times.

4.12. Discussion

4.12.1 Key findings

The results presented in this chapter corresponded to thesis objective 3.

3. To determine the cumulative incidence and incidence rates of any developmental disorder, and of individual developmental disorders, in the Born in Bradford cohort

Any developmental disorder from medical records

- The overall cumulative incidence of any developmental disorder was 11.4% (95% CI: 10.8 to 11.9%).
- The overall incidence rate of any developmental disorder was 10.0 (95% CI 9.5 to 10.4) per 1,000 person years.

Any SEND from education records

- The overall cumulative incidence of any SEND was 27.1% (95% CI: 26.3 to 28.0%).
- The overall incidence rate of any SEND was 23.0 (95% CI 22.2 to 23.8) per 1,000 person years.

Incidence rate of individual developmental disorders

- The age at the first code appearing in the medical records varied by individual disorder, therefore, in order to minimise loss of data, incidence rate was used.
- The most common disorders were speech, language and communication disorders (3.52 cases/1,000 person years), the least common was CP (0.25 cases/1,000 person years).
- The incidence rate of individual developmental disorders varied by ethnicity; White children had a higher incidence rate of ASD, ADHD, and social, emotional, and behavioural problems. Asian children had a higher incidence of hearing impairment and learning disabilities.

4.12.2 Strengths and limitations

The distribution of gestational age, and its relation to other covariates such as ethnicity is similar to national figures (e.g. early term birth is more common in deprived groups, and less common in White women), despite the lack of extremely preterm infants, which adds to the generalisability of the findings (Office for National Statistics, 2023).

Analysis cohort compared to BiB cohort

There were 13,858 children in the whole cohort and 13,172 in the main analysis cohort (see Figure 59 - Flow chart for selection of analysis cohort). This was as a result of the prespecified exclusion criteria. The characteristics of the whole cohort, the analysis cohort, and the subset with linked education data were similar, apart from multiplicity. Therefore, it is unlikely this would be a significant source of bias.

Of the children in the analysis cohort 1,680 did not have linked education records. In the subset with linked education records 17.6% of children were “least deprived and most educated” socio-economic group, whereas in the whole cohort this was 19.6%. The percentage within the benefits but coping and most deprived groups were higher, compared to in the whole cohort, and in the analysis cohort (see Table 29). Similarly, there was a higher proportion of Asian children in the education subset, compared to 52.7% in the whole cohort, and a lower proportion of White children (36.6%) in the education subset, compared to the main cohort (38.6%). This could suggest that White children, or children from the least deprived and most educated families, were more likely to move out of the area before the children started school, or that these families were more likely to choose to send their children to schools out of area, or to private school. This could be a source of selection bias.

Determining gestational age

The majority of women had ultrasound scans in pregnancy to determine the gestational age. Thus, there can be relative confidence in the accuracy of the exposure variable. However, it is possible that there was a pattern to the women who had not had a dating scan, which was not investigated.

Measurement of disease burden

Within the main analysis cohort there were 53 deaths and 324 withdrawals. These children’s data were included up until the point of death/withdrawal. Data on the causes of death were unavailable. For the primary outcome cumulative incidence was chosen as the measure of disease

outcome. This does not consider deaths or withdrawals, but was chosen as the simplest measure, and the most intuitive for clinicians and other professionals (e.g. educationalists) to understand.

Timing of outcome measures

At the point of the primary care data extract, the children were aged 11-15 years. There were 219 children (out of 13,172 = 1.7%) who were 11 at the point of data extract. However, 35 (15.9%) of these already had a code related to developmental disorder in their primary or secondary care records. This is higher than the total cumulative incidence therefore it seemed unlikely there would be more incident cases in the remaining months before those children's 12th birthdays. An alternative approach would have been to remove these children from the analysis cohort, or to censor the data at the 11th birthdays, but this would have led to loss of data.

BiB were unsure precisely when the SEND data was collected, stating that it could be "anywhere between the first term and the end of the year". The data is sent to BiB on the 31st July every year. A date in the middle of year (March) was therefore chosen as the date for the outcome, and since this was consistent it would be unlikely to introduce bias. Similarly, the children's dates of birth were not given, in order to preserve anonymity, so approximately birthdates were used.

The timing of onset of the signs or symptoms corresponding to a particular developmental disorder cannot be determined using these methods. The date of the clinical code is the time at which the code first appeared in the child's medical records, not when the signs or symptoms first appeared. However, since this is the method used throughout the secondary data analysis this is unlikely to have introduced bias.

Children <30 weeks will have routine developmental follow-up as per the NICE guidelines, for other children it will rely on their parents to seek medical advice if there are concerns about their development. This could have inflated the cumulative incidence of developmental disorder amongst the very preterm children within the cohort, compared to the other gestational age groups.

Grouping of codes

The calculation of the incidence rates of individual groups of developmental disorders, as well as the latent class analysis (see chapter 6), relies upon the meaningful grouping of clinical codes. This was largely done based on previous lists and the hierarchical nature of the coding structure. Where there were uncertainties, these were discussed with clinicians. However, the grouping could have been done differently which might have produced different results, for example, codes relating to 'delay' were, where possible grouped with the corresponding disorder, as opposed to

the 'developmental delay' category; "Motor developmental delay" and "Speech delay" were grouped with "motor function disorders" and "Speech, language, and communication" disorders respectively, not "Developmental delay". This was chosen because developmental delay is non-specific and may have been less useful to clinicians and parents. Some of the groups of codes were very broad, and this may limit their use; "Speech, language and communication" problems could include children without communicative intent as well as codes such as speech impairments, which have a different pathophysiological pathway. Whilst this thesis aimed to have a holistic, comprehensive approach and sought to include all the developmental disorders children might face, this was not always possible: there were only three occurrences of ICD-10 codes corresponding to executive function problems ("Other and unspecified symptoms and signs involving cognitive functions and awareness") and no relevant CTV3 codes, and so these were subsequently reassigned into the "learning disability" group, in order to make use of the data.

4.12.3. Chapter summary

This chapter has described the selection of the analysis cohort and its characteristics. The factors associated with the exposure (gestational age) have been explored. These were largely as expected. The relationship between ethnicity and other covariates were explored. The cumulative incidence of developmental disorders in medical records (both primary and secondary care) and SEND in education records has been calculated and the intersection between them explored. The incidence rate of developmental disorders in medical records (primary and secondary care combined) and SEND in education has been calculated. The prevalence of SEND in education records by academic year has been calculated. The subsequent chapter will explore how the cumulative incidence and incidence rate of developmental disorders is associated with neonatal, antenatal, and socio-demographic factors, and investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models.

Chapter 5: Results 2 - Factors associated with Developmental Disorders in the Born in Bradford cohort: Statistical Modelling

5.1. Introduction

The results presented in this chapter correspond to the following thesis objectives:

3. To explore how the cumulative incidence and incidence rates of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity
4. To investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models

These results are based on the analysis cohort whose selection is described in Chapter 3 - methods, and Chapter 4 – results 1. The first half (section 5.3) of this chapter presents univariable statistical modelling with the outcome of cumulative incidence of developmental disorder by age 12 (section 5.3.1) and then cumulative incidence of Special Educational Needs and Disabilities (SEND) up to and including year 7 (section 5.3.2). The incidence rates of developmental disorders and of SEND by the same characteristics is presented as appendices (appendix 5.1 and 5.2).

Finally, the results of the multivariable statistical modelling investigating how the cumulative incidence of developmental disorders section (5.4.1) and then the cumulative incidence of SEND (5.4.2) varies according to gestational age when adjusting for key covariates are presented.

Throughout these analyses developmental disorders within the medical records and Special Educational Needs and Disabilities (SEND) within the education records are considered as separate outcomes. The NICE guideline for the developmental follow-up of children and young people born preterm includes SEND as one of the outcomes children born preterm are at risk of, and thus it could have been merged into a single outcome for the analyses. However, considering its much higher incidence, its different source, and the fact it includes conditions which are not developmental disorders (e.g. “mental health difficulties”), the decision was taken to consider it separately, which will also allow comparison between the two outcomes.

5.2. Variables of interest

Figure 75 is a figurative representation of the putative relationships between the exposure (gestational age), the outcome (developmental disorder), and potential confounders and mediators, introduced in section 1.3.1. Some of the variables and their potential interactions have been blacked out when they could not be investigated further; data on maternal mental health is not presented, since this was collected during the children's primary school years, i.e. when the children were older than the average age at which the first diagnostic codes appear in the medical records. Data on neonatal illness were not available; initially the 'admission to special care' variable was considered as a proxy marker for neonatal illness, but this was not considered a viable option since admission to special care is so closely linked to gestational age, and there were concerns about the quality of this variable (see section 4.4.1. Neonatal characteristics).

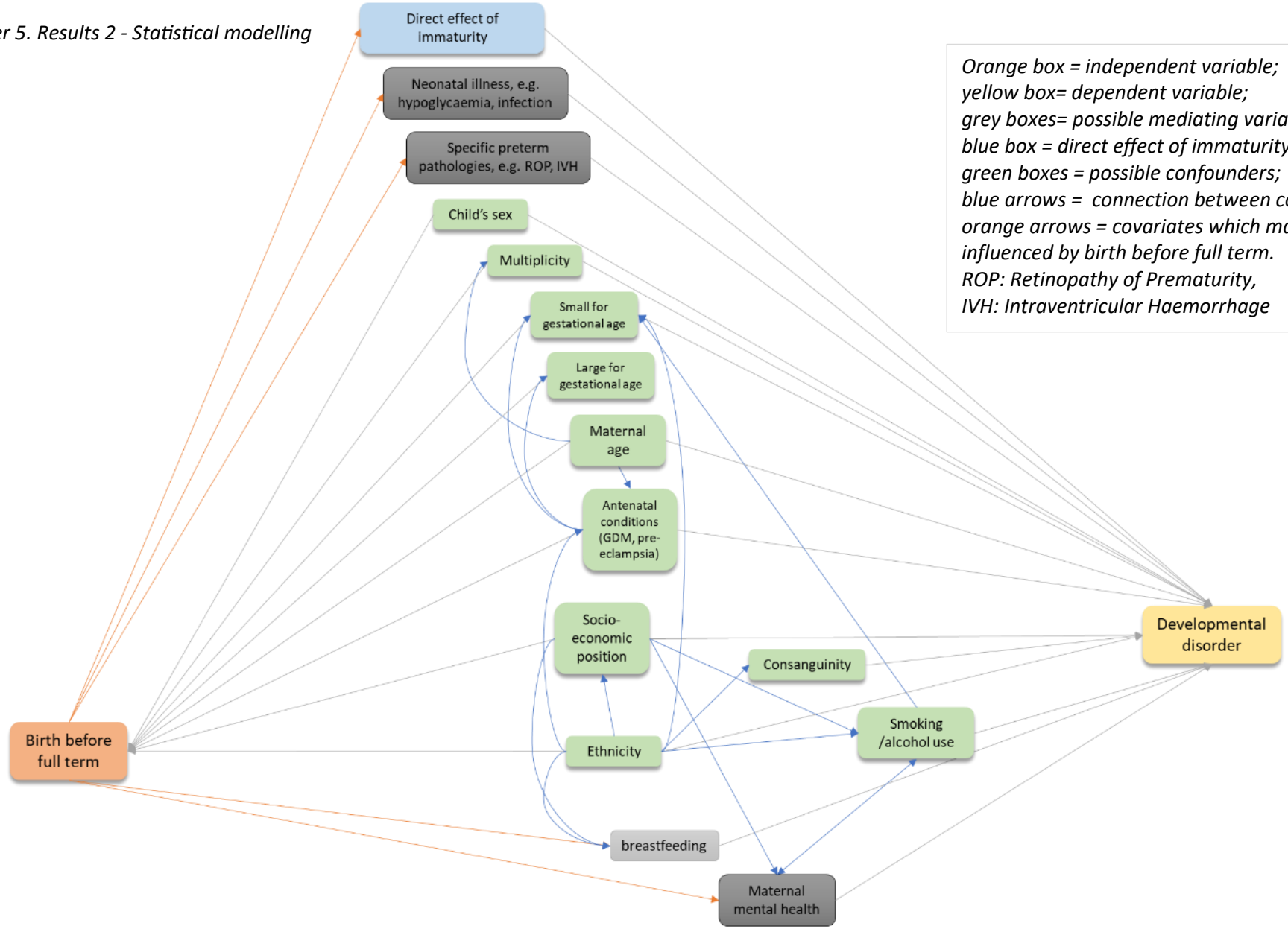


Figure 75 - Figurative representation showing possible associations between birth before full term, developmental disorder and covariates

5.3. Univariable statistical modelling

This section corresponds to the following objective:

> 4. To explore how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity

As discussed in section 4.6, the cumulative incidence of developmental disorder calculations used a cut off of the children's approximated 12th birthday in their medical records. The cumulative incidence of special educational needs and disabilities (SEND) in education includes records up to (and including) year 7 (children will turn 12 before the end of year 7). Participants' characteristics dichotomised by outcome are presented, first by cumulative incidence of developmental disorder (in medical records) see section 5.3.1, then by special educational needs and disabilities (in education records). These findings are summarised in Table 54 in section 5.3.3.

The variation of incidence rate of developmental disorders according to all the variables of interest are presented as appendices (appendix 5.1 and 5.2).The variation of the incidence rate of individual developmental disorders with gestational age is presented in section 5.3.5 below, but relationships with other variables were not explored further, due to small numbers.

5.3.1. Characteristics by outcome: Cumulative incidence of developmental disorder up to 12th birthday in medical records

The characteristics of the participants dichotomised by outcome, cumulative incidence of developmental disorder up to 12th birthday in medical records, are described below, and in the tables in appendix 5.1. These are displayed graphically where variables have multiple categories.

Neonatal Characteristics

There was a reverse "J shape" relationship between gestational age and the cumulative incidence of developmental disorder (the incidence of developmental disorder decreases with gestational maturity, but then there was a sharp uptick post term. The 95% confidence intervals (green dashed lines) also widen at both ends of the graph, due to smaller numbers of children in those categories (confidence interval values are shown in appendix 5.3).

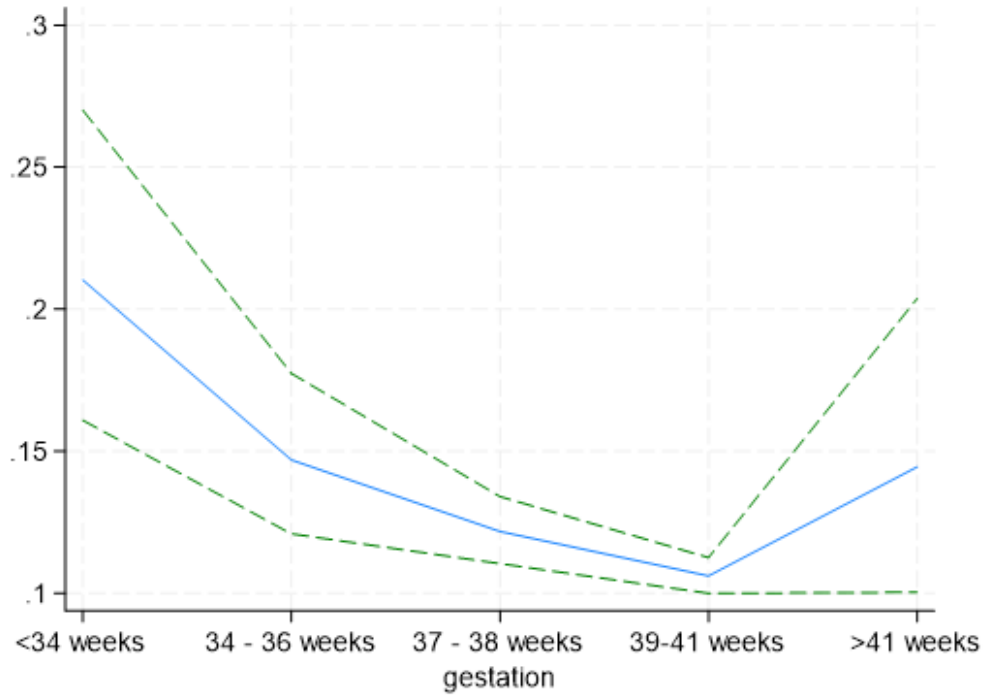


Figure 76 - Cumulative incidence of developmental disorder by gestational age.

Developmental disorders were substantially more common in boys than girls (14.8% vs 7.7% respectively). There was no difference in cumulative incidence of developmental disorders in singletons compared to twins. Children born SGA had a cumulative incidence of developmental disorders of 13.2% compared to 11.1% in those who were not born SGA.

Antenatal Characteristics

Maternal age at the child's delivery was transformed from a continuous to a categorical variable. The lowest cumulative incidence was seen in the mothers aged 31-35 years at delivery (10.3%); the highest incidence was seen in the group where mothers were >35 at delivery (13.5%) (Figure 77). It follows a similar pattern to that seen for gestational age, backwards J, just less pronounced and with less variation between age bands.

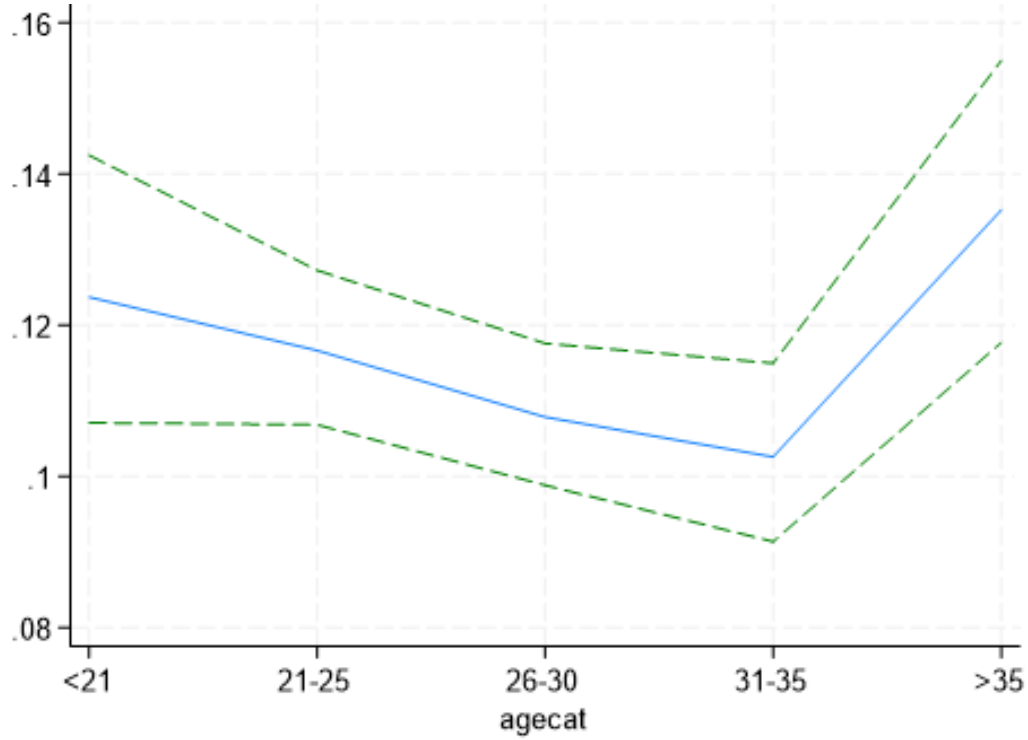


Figure 77 - Cumulative incidence of developmental disorder by maternal age at child's birth. Green dashed lines indicate 95% confidence intervals

The cumulative incidence of developmental disorders in children born to women who had gestational diabetes, or pre-eclampsia does not appear substantially different that those who were not.

Socio-demographic characteristics

The cumulative incidence of developmental disorders appears to be proportional to deprivation; the most deprived group has the highest cumulative incidence of developmental disorder (13.4%), and the least deprived group has the lowest (8.9%) (Table 81 and Figure 78)

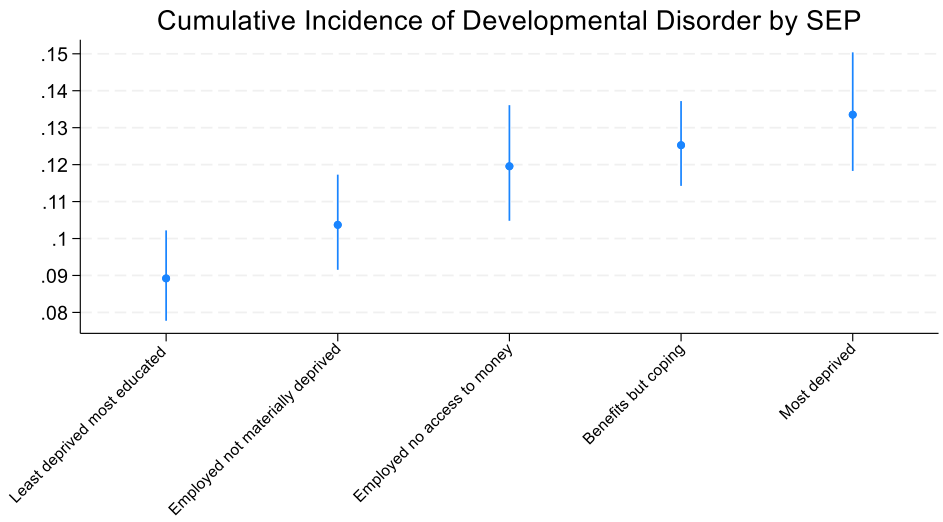


Figure 78 - Cumulative incidence of developmental disorder by socio-economic position (SEP) measured by five group latent class analysis.

Vertical lines show 95% confidence intervals.

The highest cumulative incidence of developmental disorder was amongst White children (12.5%), see Figure 79. The cumulative incidence was lower in the Asian (10.8%), Black (8.2%) and 'Other' ethnic groups.

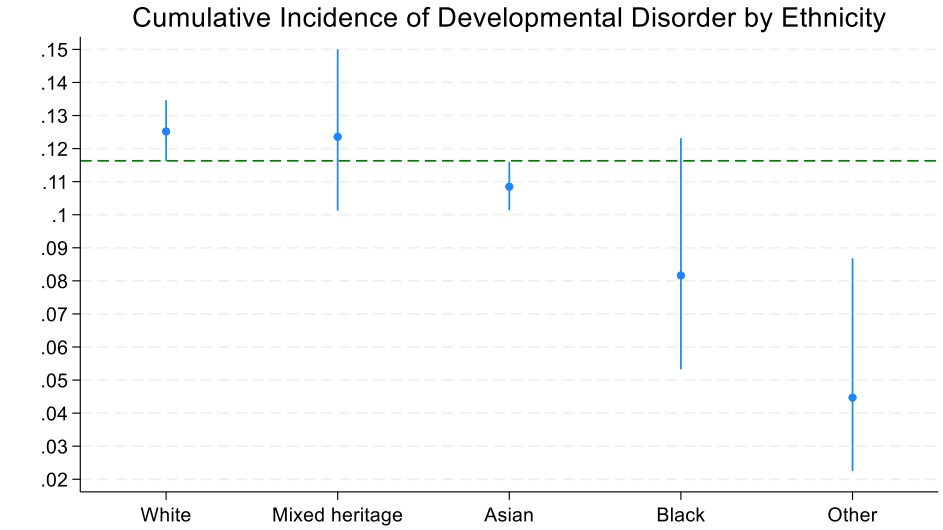


Figure 79 - Cumulative incidence of developmental disorder by child's ethnicity. Green dashed line shows lower bound of 95% confidence interval in White group

The relationship with socio-economic position was different for the two largest ethnic groups (see Figure 80); in the White group the cumulative incidence of developmental disorder increases with increasing deprivation (8.3% to 16.3%), with the least deprived group having nearly double the incidence of developmental disorders compared to the least deprived. In the Asian group the cumulative incidence of developmental disorder was relatively unchanged with socio-economic position; the lowest incidence is in the least deprived and most educated group (9.4%), but the highest incidence (12.9%) was seen in the 'employed not materially deprived' group.

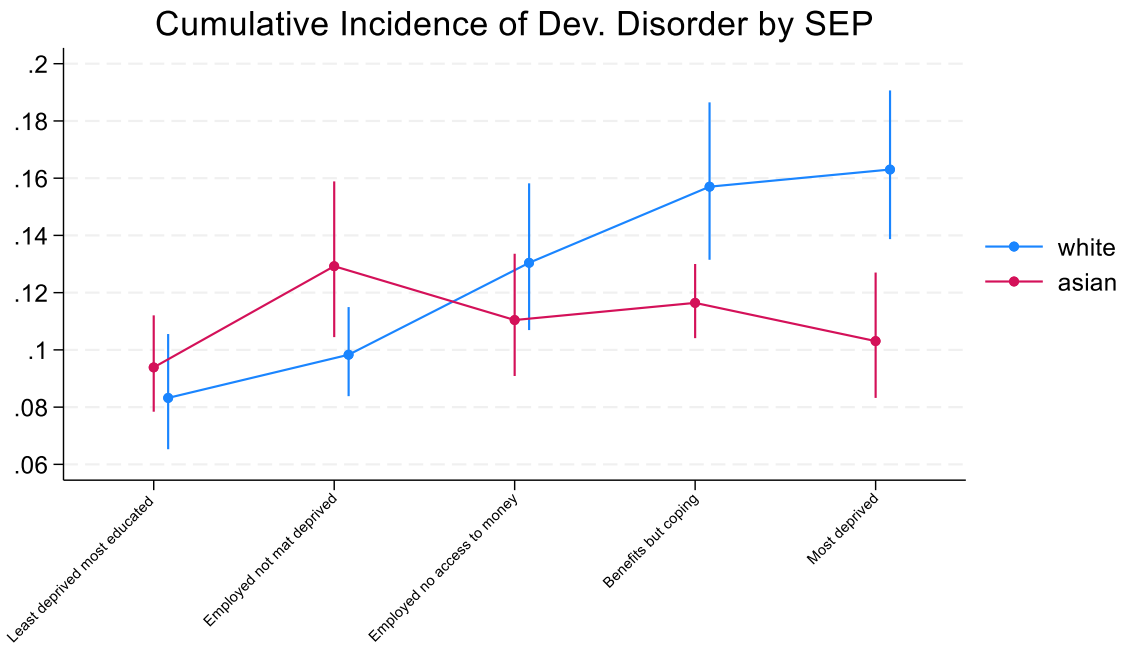


Figure 80 - Cumulative incidence of developmental disorder by socioeconomic position (SEP) for White and Asian children. Dot shows estimate and vertical lines show 95% confidence intervals

Postnatal characteristics

The proportion of children with developmental disorder was lower in the group where the child was ever breast fed, compared to the children who were not (10.7% compared to 13.6%). However, it should be noted that these data were missing for over 50% of the analysis cohort.

5.3.2. Characteristics by outcome: Cumulative incidence of Special Educational needs and disabilities in education records up to (and including) year 7

Neonatal characteristics

The table and graph below show the relationship between gestational age and the cumulative incidence of SEND in education records, up to and including Year 7. The lowest cumulative incidence of SEND is in the full term (39-41 weeks) group (25.9%), as with developmental disorder from medical records (Figure 81). The highest cumulative incidence is in the <34 weeks group (41.2%) and then the 34-36 weeks group (36.4%). The general trend is a reduction in cumulative incidence of SEND as gestational increases until 41 weeks with a slight increase seen in those born >41 weeks.

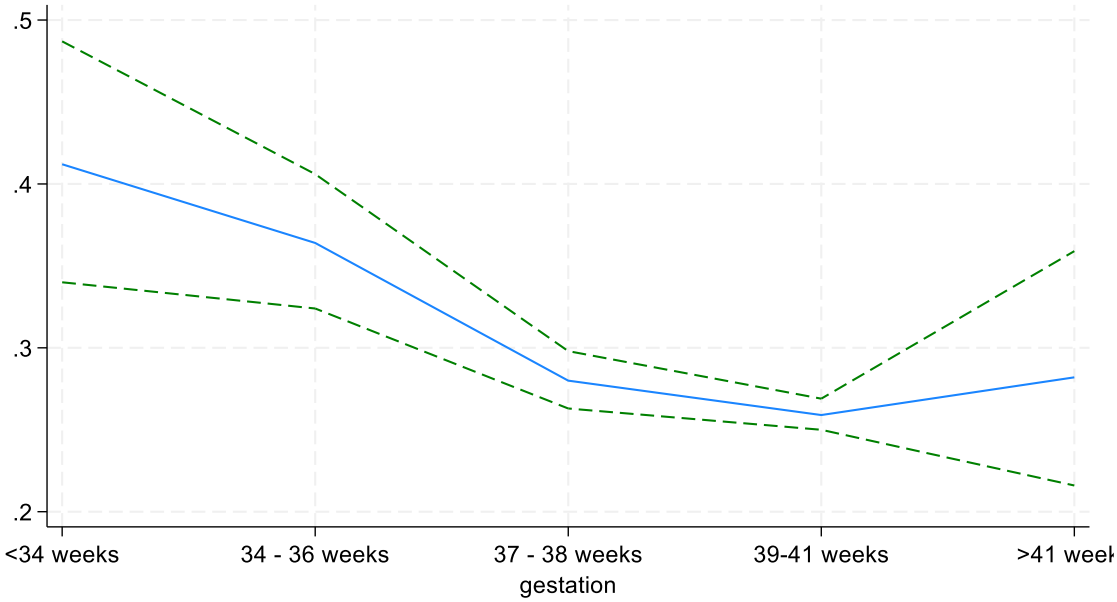


Figure 81 - Cumulative incidence of Special Educational Needs and Disability by gestational age. Green dashed lines indicate 95% confidence intervals

The cumulative incidence of SEND was much higher in boys than girls (34.1% vs. 19.8%). It was also more common if the child had been born SGA compared to not SGA (32.0% vs. 26.3%). However, the cumulative incidence of SEND amongst singletons and twins was similar (27.1% vs. 27.8% respectively).

Antenatal characteristics

As with developmental disorders from medical records, the lowest cumulative incidence is seen in the mothers aged 31-35 years at delivery (24.2%), however unlike with developmental disorders, the highest cumulative incidence was in the group <21 years old at delivery (32.8%) (not the group >35 years old), see Figure 82.

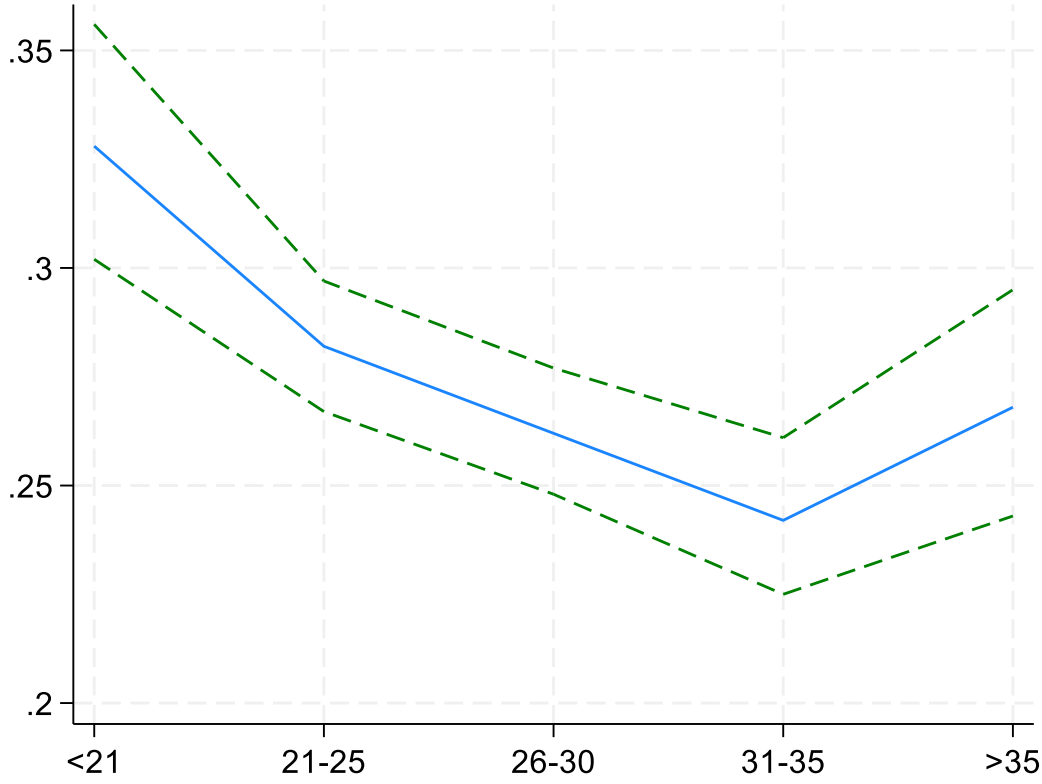


Figure 82 - Cumulative incidence of SEND by maternal age (years) at child's birth. Green dashed lines indicate 95% confidence intervals

Socio-demographic characteristics

Like developmental disorders in medical records, the cumulative incidence of SEND in education records appeared to be proportional to deprivation, however for SEND the relationship was even more pronounced; the cumulative incidence of SEND in the most deprived group (36.7%) was almost double the highest cumulative incidence of SEND in the least deprived group (18.8%) (compare Figure 78 and Figure 83).

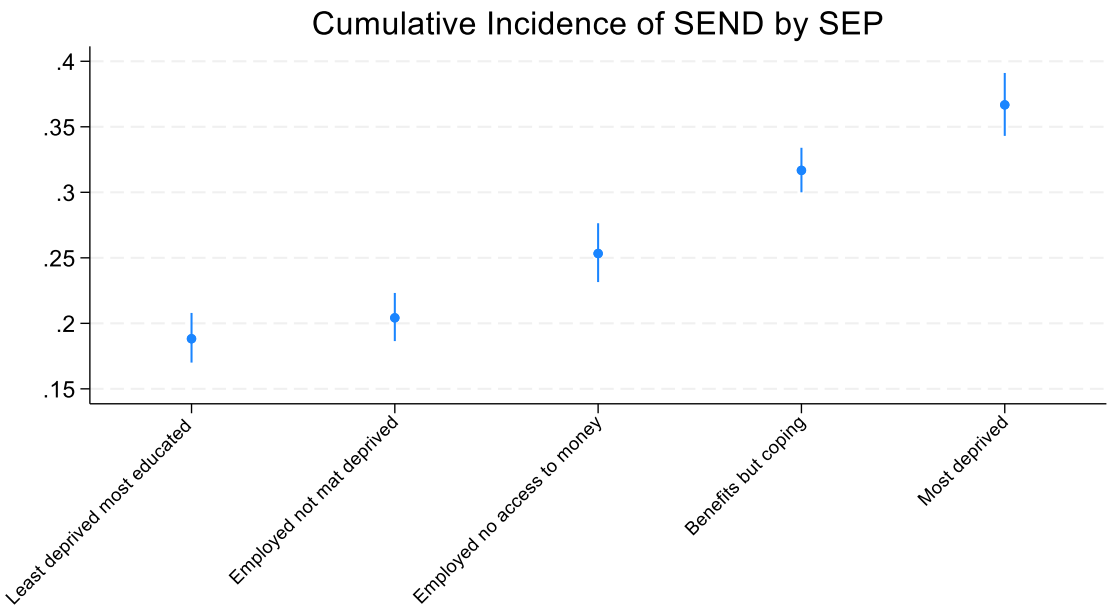


Figure 83 - Cumulative incidence of Special Educational Needs and Disability (SEND) by Socio-economic position (SEP) measured using five group latent class analysis

Similar to the pattern seen with developmental disorder from medical records, the cumulative incidence of SEND was highest in the White group (28.8%), see Figure 84. Although the cumulative incidence of SEND was lower in the Asian group (25.6%) than the White group the confidence intervals overlap slightly. The lowest cumulative incidence was seen in the 'other' group (13.2%), but note this group is very small.

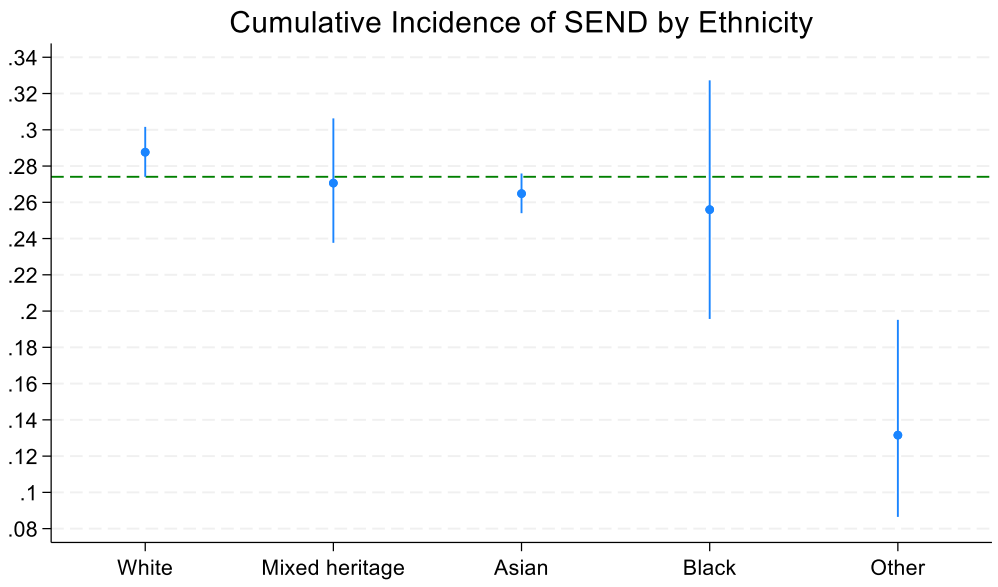


Figure 84 - Cumulative incidence of Special Educational Needs and Disability (SEND) by ethnicity

The proportion of children with SEND according to socioeconomic position for White children and for Asian children was shown in Table 88 and Figure 85. The cumulative incidences were similar for the two ethnic groups in the "least deprived most educated" group, but then they diverge as the deprivation increases, although the patterns are similar. The cumulative incidence doubles in the White group from the least to most deprived (from 19.7% to 40.9%); whereas in the Asian children the increase from the least deprived to most deprived is not as pronounced (16.3% to 28.8%).

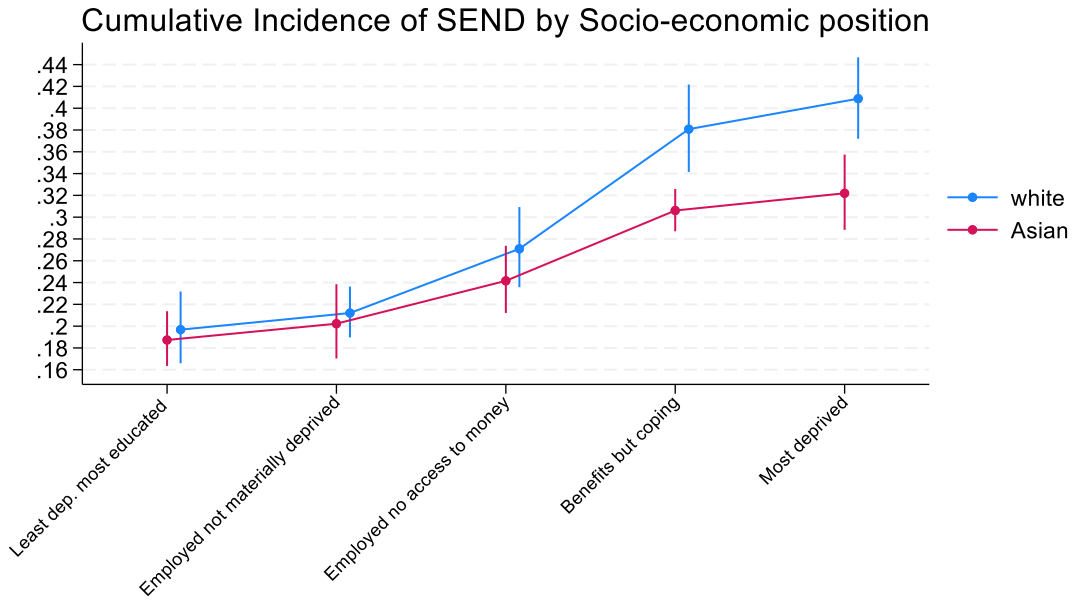


Figure 85 - Cumulative incidence of special educational needs and disabilities (SEND) by socioeconomic position for White children and Asian children

5.3.3. Summary of factors associated with cumulative incidence of developmental disorder (in medical records) special educational needs and disabilities (in education records)

The relationships between the variables and the two outcomes (developmental disorder and SEND) are largely the same, apart from Mother's age at birth, index of multiple deprivation and Alcohol in first 3 months of pregnancy (Table 54). The graphs from the previous section are condensed to allow comparison in Figure 86.

Table 54 - Summary of associations between gestational age and variables of interest and cumulative incidence of developmental disorder from medical records, and of special educational needs and disabilities (SEND) in education records.

	Developmental disorder	**SEND**
NEONATAL FACTORS		
Gestational age	Least common at full term	Least common at full term
Child's sex	More common in boys	More common in boys
Multiplicity	nil	nil
Small for gestational age (SGA)	More common if SGA	More common if SGA
ANTENATAL FACTORS		
Mother's age at child's birth, categorised	Least common in 31-35 year group, most common in >35 year group	Least common in 31-35 year group, most common in <21 year group
Pre-eclampsia	nil	nil
Gestational diabetes	nil	nil
SOCIO DEMOGRAPHIC CHARACTERISTICS		
Socio-economic Deprivation - five group latent class	Least common in least deprived group	Least common in least deprived group
Index of Multiple Deprivation group	nil	Least common in least deprived group
Means tested benefits (MTB)	More common if received MTB	More common if received MTB
Mother's highest educational qualification	Least common in most educated group	Least common in most educated group
Child's ethnicity	Most common in White group	Most common in White group
Consanguinity	More common if consanguineous	More common if consanguineous
Alcohol in first 3 months of pregnancy	nil	More common if alcohol in first 3m
Alcohol since 4th month of pregnancy	nil	nil
Smoking during pregnancy	More common if smoked	More common if smoked
POSTNATAL FACTORS		
Breastfeeding	Less common if breastfed	Less common if breastfed

Nil = not statistically significant, although there may have been a non-statistically significant relationship demonstrated.

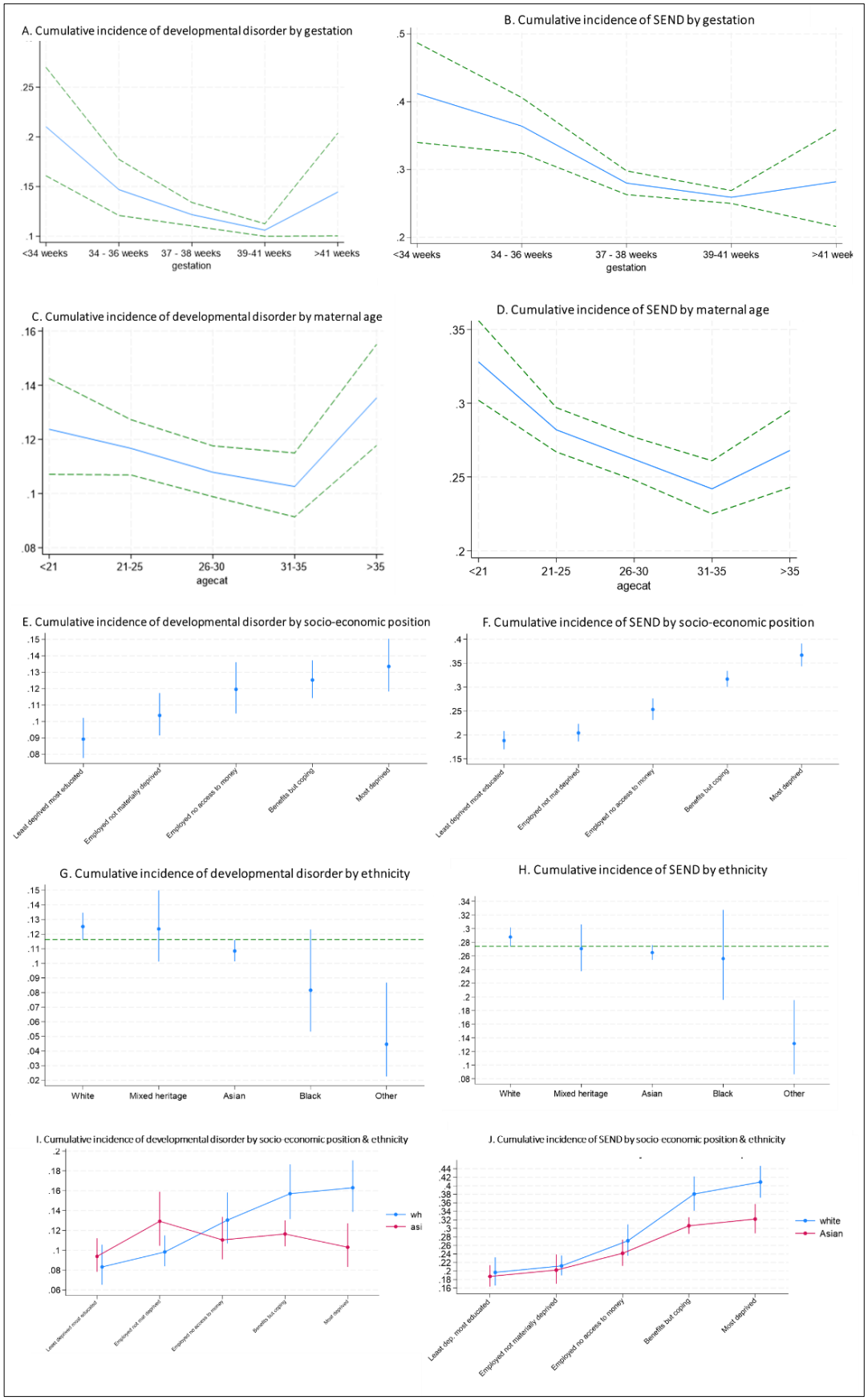


Figure 86 - Cumulative incidence of developmental disorder up to age 12 (left side) and Special Educational Needs and Disability (SEND) up to (and including) Year 7 (right side) according to gestational age and covariates.

5.3.4. Incidence rate of developmental disorder and Special Educational Needs and Disability (SEND)

Developmental disorders from medical records

As described in Chapter 4 – Results 1, there was a total of 1,640 incident codes corresponding to a developmental disorder within the medical records, and 164,823.2 person years. This equates to an incidence rate of 10.0 (95% CI 9.5 to 10.4) per 1,000 person years. The variation of incidence rate according to the covariates of interest is shown in appendix 5.4.

Special Educational Needs and Disability in education records

There was a total of 3,188 incident records of Special Educational Needs and Disability in education records and 138,778.3 person years. This equates to an incidence rate of 23.0 (95% CI 22.2 to 23.8) per 1,000 person years. The variation of incidence rate according to the covariates of interest is shown in appendix 5.5.

The relationship between the covariates of interest and the outcomes (developmental disorders from medical records and Special Educational Needs and Disability in education records) were similar to when cumulative incidence is used as the measure of disease burden. The only change was that the difference between the incidence rate of developmental disorders between Asian and White children was more clear, White 11.63 (95% CI 10.82 to 12.51) per 1,000 person years, vs. Asian 9.02 (8.41 to 9.67) per 1,000 person years, whereas when cumulative incidence was used the confidence intervals almost overlap. White children 12.5% (11.6% to 13.5%), Asian children 10.8% (10.1% to 11.6%). This is likely reflective of the different types of developmental disorder which are most common amongst White compared to Asian children; White children had a higher incidence rate of ASD, ADHD, and social, emotional, and behavioural problems compared to Asian children (see section 4.9.3), and these three disorders had the highest median ages of first code, compared to the other disorders explored in this thesis. Thus, using the cumulative incidence measure, with the cut off at age 12, made the apparent difference in disease burden between the two ethnic groups less clear.

5.3.5. Incidence rate of individual developmental disorders, by gestational age

When exploring the relationship between individual developmental disorders and gestational age, incidence rate was used in order to minimise loss of data. There were fewer than 100 cases in the analysis cohort of six of the different developmental disorders explored (see section 4.9.2. Incidence rate of each disorder); for example, 44 incident cases of CP, and 76 incident cases of hearing impairment. Therefore, multivariable modelling of the association between individual developmental disorders and gestational age was not possible. However, univariable analysis showed that the incidence rate of some developmental disorders varied with gestational age (see Table 95 and Figure 87). There was a clearer association with gestational age for some disorders (such as CP and developmental delay) than there was with other disorders (e.g. ASD and ADHD), which appear to have an almost 'flat' line graph because the numbers of cases of individual disorders were quite small, and confidence intervals at the extremes of gestation are wide.

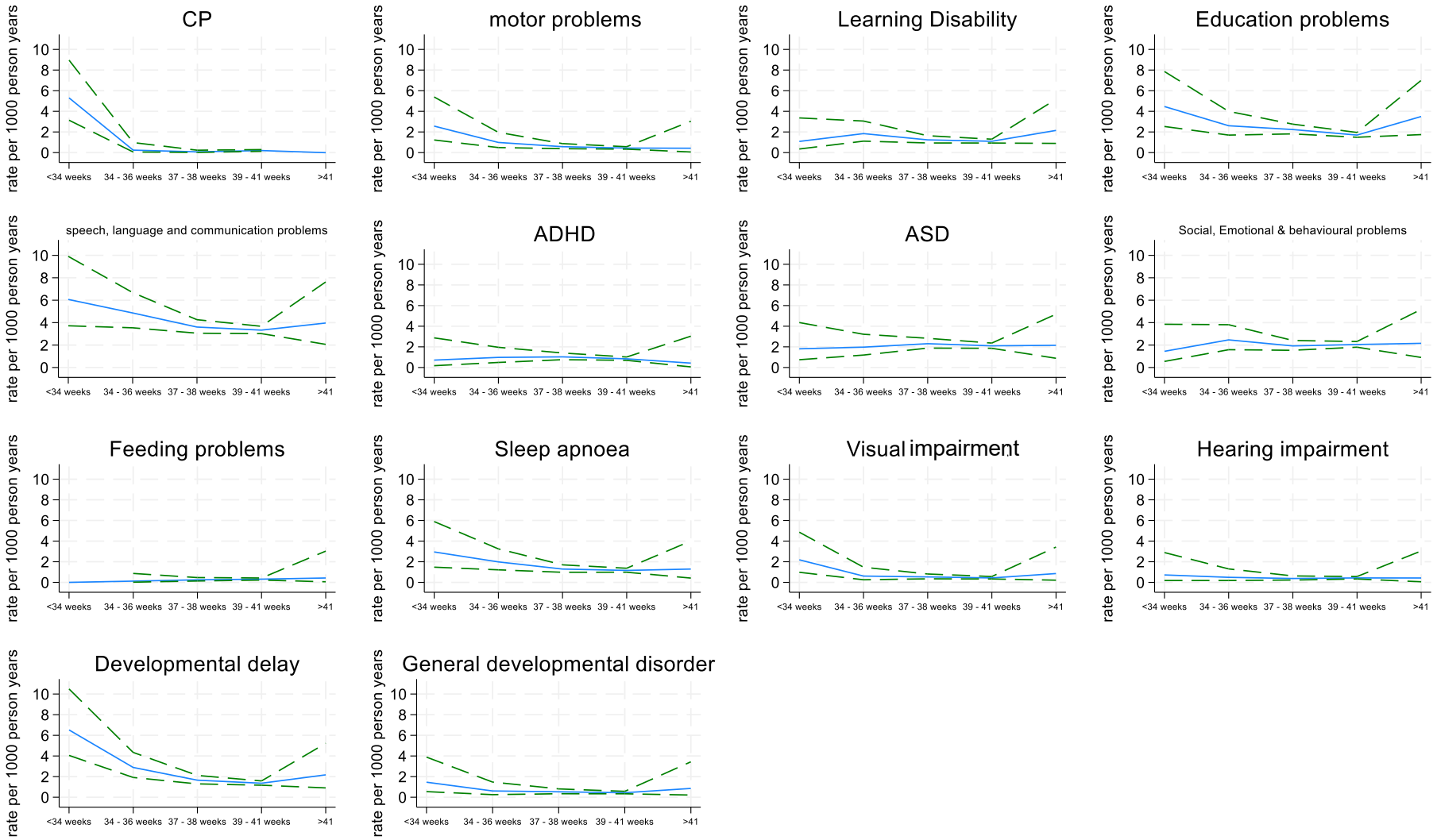


Figure 87 - Incidence rate of groups of developmental disorders according to gestational age

5.4. Multivariable statistical modelling

This section corresponds to the following objective:

> 5. To investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models

Cumulative incidence of developmental disorders from medical records and cumulative incidence of special educational needs and disabilities (SEND) were both explored. Section 5.4.1 relates to developmental disorders in medical records, and section 5.4.2 relates to SEND within education records.

Covariates of interest

Pre-eclampsia, gestational diabetes and small for gestational age (SGA) can be considered measures of in utero compromise. Pre-eclampsia and gestational diabetes were not included in multivariable modelling as they were highly correlated with SGA (pre-eclampsia and SGA correlation co-efficient 0.07, p: <0.0001; GDM and SGA correlation co-efficient -0.04, p: 0.0001, see Table 55 below). SGA was chosen as the preferred proxy measure of in utero compromise; both gestational diabetes and pre-eclampsia can be variable in terms of their impact on the mother and fetus. Consanguinity is highly correlated with ethnicity (as shown in Chapter 4 – Results 1, and below in Table 55, correlation co-efficient 0.51, p:<0.001), and so will not be included further. Data on breastfeeding and alcohol consumption had over 50% of responses missing and therefore were not included in any further analyses. As mentioned at the start of this chapter, useful data on maternal mental health and neonatal illness were not available. This left the remaining variables to be investigated for inclusion in the multivariable model. The relationships are shown in the reduced figurative representation below (Figure 88), which is then followed by a table of correlation coefficients.

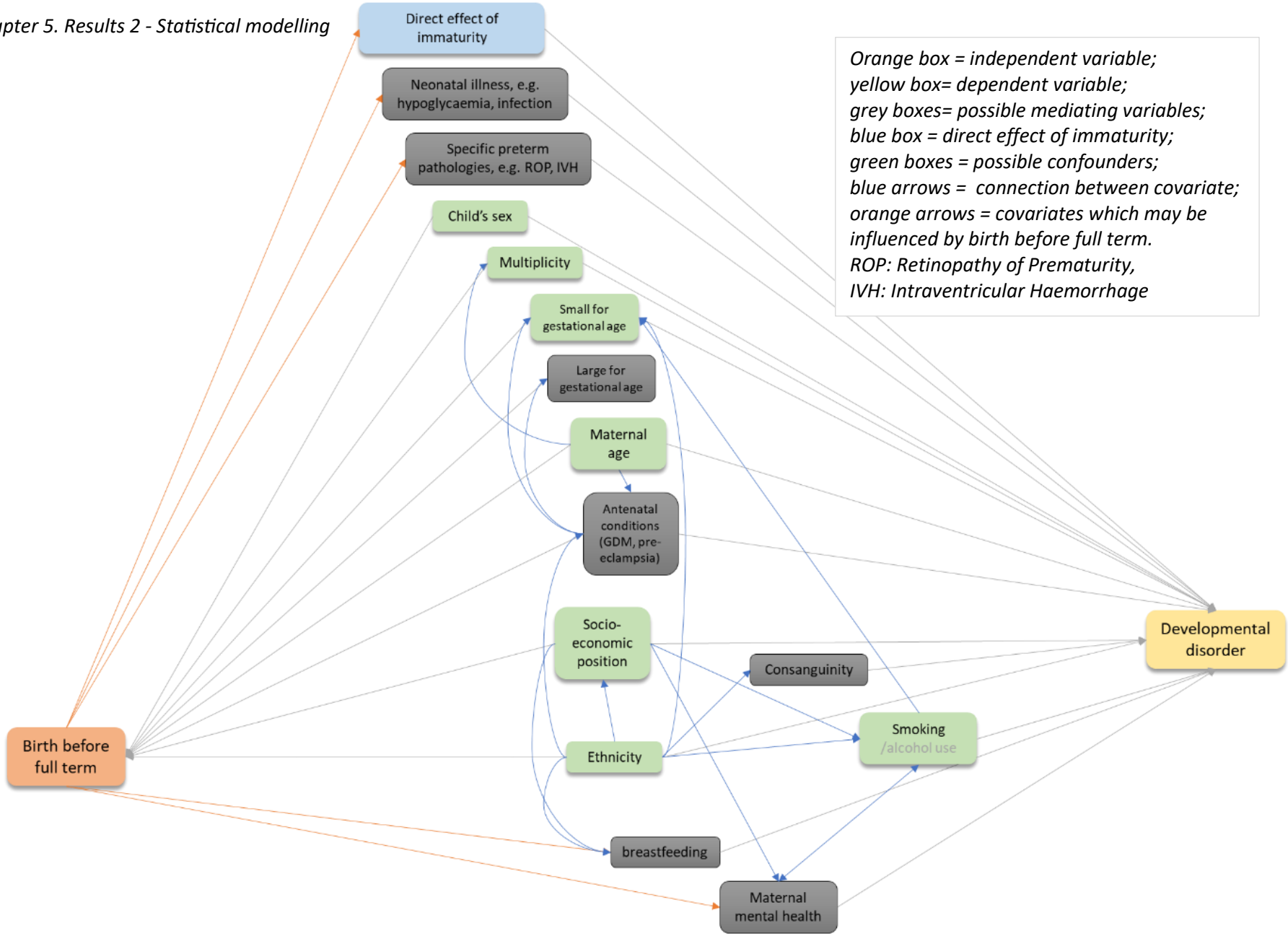


Figure 88 - Reduced figurative representation showing possible associations between exposure (birth before full term), outcome (developmental disorder) and covariates

Table 55 - Correlation coefficients of variables of interest and corresponding p-values underneath

	GA	Child's sex	Multiplicity	SGA	Mother's age	Pre-eclamp.	GDM	SEP - LCA	IMD	MTB	Mat. Edu.	Ethnicity	Consanguinity	Smoking
Gestational age	1													
Child's sex	0.02	1												
Multiplicity	-0.27**	0.010	1											
SGA	0.05*	0.01	.	1										
Mother's age	-0.06**	-0.007	0.036**	-0.05**	1									
Pre-eclampsia	-0.15**	0.00	0.05**	0.07**	0.013	1								
Gestational diab. (GDM)	-0.21**	-0.002	0.04**	-0.04**	0.16**	-0.003	1							
SEP - 5 group LCA	-0.01	0.036**	-0.01	0.04**	-0.17**	-0.00	0.01	1						
IMD	0.01	-0.00	0.02	-0.06**	0.16**	0.01	-0.02	-0.30**	1					
Means tested benefits(MTB)	0.02*	-0.01	-0.01	0.02	-0.02*	0.03**	-0.02*	-0.51**	0.19**	1				
Maternal education	0.01	-0.02*	0.00	-0.04**	0.19**	-0.00	-0.01	-0.56**	0.21**	0.25**	1			
Child's ethnicity	-0.03*	0.01	0.00	0.10**	0.11**	-0.01	0.10**	0.08**	-0.30**	-0.07**	-0.004	1		
Consanguinity	-0.02	0.01	0.01	0.10**	0.02*	0.01	0.08**	0.18**	-0.22**	-0.12**	-0.17**	0.51**	1	
Smoking	-0.02	-0.01	-0.01	0.03**	-0.22**	-0.03*	-0.06**	0.20**	-0.04**	-0.11**	-0.18**	-0.36**	-0.25**	1

** indicates p value <0.05, ** p <0.001. SGA: small for gestational age, LCA: latent class analysis, MTB: receipt of means tested benefits, GDM: gestational diabetes. SEP: socio-economic position, IMD: index of multiple deprivation*

5.4.1. Modelling the relationship between gestational age and the cumulative incidence of developmental disorder

Before adjusting for covariates, four different options for modelling the relationship between gestational age and cumulative incidence of developmental disorder up to the 12th birthday were explored. These were adapted from those described by Richards (20016) et al. (Richards et al., 2016a), as follows:

(1) Continuous linear model
(2) Continuous adding a quadratic term
(3) Categories for each week of gestation compared to a 40-week reference category
(4) Categorising gestational age groups and comparing to a full term reference category

Options 1 -3 are presented in appendix 5.7. The fourth option (categorising gestational age groups and comparing to full term reference category) was chosen because it allowed use of all the data, the odds ratio can increase post term, and it does not result in extremely small categories, and it is also clinically relevant, as these groups reflect how babies are managed on neonatal units and postnatal wards.

Table 56 - Odds ratio of developmental disorder from logistic regression, with gestational age categories, compared to full term reference category

Gestational age categories, weeks	odds ratio	95% confidence interval		P-value
<34 weeks	2.24	1.60	3.14	<0.001
34 - 36 weeks	1.45	1.15	1.83	0.002
37 - 38 weeks	1.17	1.03	1.33	0.02
39 – 41 weeks	1.00 (Reference category)			
>41 weeks	1.42	0.93	2.17	0.1

Number of observations = 13,172

5.4.1.2. Modelling the relationship between gestational age and the incidence rate of developmental disorder

The previous regression analysis used the binary outcome of cumulative incidence of a developmental disorder by the child's 12th birthday. An exploratory analysis was carried out to see if similar results would be obtained if Poisson regression were used, the results are presented in appendix 5.8. This approach has the advantage of using all the available data, without imposing a cut-off point at a specific age. The results were over dispersed, so negative binomial regression was used (Fávero, Belfiore, Santos et al., 2020). The incidence rate ratios were similar to the odds ratios from the final logistic regression model shown in section 5.4.1.3 below. Therefore, for simplicity and ease of interpretation, logistic regression, using the binary outcome of any developmental disorder by the approximated 12th birthday, will be used for all remaining analyses.

5.4.1.3. The multivariable model - Odds of developmental disorder by 12th birthday.

Initially a complete case analysis was carried out (see appendix 5.9), where only participants with complete data for the relevant variables were included. The modelling strategy was largely based on the conceptual model but also considering collinearity; multiplicity was omitted due to collinearity. Following this, tests of multicollinearity on the full model (without multiplicity) were carried out and there were no variance inflation factors >5, suggesting no problematic multicollinearity (Daoud, 2017). Goodness of fit, model discrimination and influential covariate patterns and outliers were investigated, but the results of which did not require changes to be made to the model (see appendix 5.10).

Interaction terms

Interaction terms between gestational age and all the other covariates of interest were included in the model. The only one which was statistically significant was gestational category and child's sex, but that was only for the < 34 week category, therefore, no interaction terms were included in the final model.

Missing data and imputation

The amount of missing data in each covariate is presented in Table 27 - Table 30. Overall, 20% of the children in the analysis cohort had missing data for at least one of the remaining variables of interest i.e.:

- Child sex
- Small for gestational age
- Maternal age
- Five group latent class analysis (as a measure of socio-economic deprivation)
- Child's ethnicity
- Smoking in pregnancy

Patterns of missingness were explored. Auxiliary variables were considered. Pre-eclampsia, gestational diabetes, consanguinity, and maternal parity were associated with the odds of missingness in at least one of the analyses. Therefore, they were included in the imputation as auxiliary variables. Twenty five imputations were carried out, this exceeded the overall percentage of missing data (White, Royston and Wood, 2011). Further detail, and imputation diagnostics, are presented in appendix 5.12. The category with the lowest incidence of developmental disorder was used as the reference for each variable (e.g. female for child's sex).

The final adjusted imputed model – developmental disorder

The effect of gestational age remains statistically significant when adjusting for covariates; the results are almost identical to the unadjusted model (see Table 56). The odds ratios in the adjusted imputed model (Table 57) are similar to the complete case analysis (appendix 5.9), except the odds reduced slightly in the <34 week group but increased in the 34-36 week group.

Table 57 - Odds ratio of developmental disorder by gestational age. Imputed model.

	Odds ratio	95% confidence interval		P value
Gestational age				
<34 weeks	2.22	1.58	3.12	<0.001
34 - 36 weeks	1.43	1.12	1.81	0.003
37 - 38 weeks	1.18	1.03	1.34	0.02
39-41 weeks	1.00 (reference)			
>41 weeks	1.39	0.91	2.13	0.1
Child's sex				
Male	2.09	1.87	2.35	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.25	1.08	1.46	0.004
Maternal age (in years) at child's delivery				
<21	1.03	0.83	1.29	0.8
21-25	1.10	0.93	1.29	0.3
26-30	1.04	0.89	1.23	0.6
31-35	1.00 (reference)			
>35	1.35	1.10	1.66	0.005
Socio-economic position				
Most educated, least deprived	1.00 (reference)			
Employed not materially deprived	1.08	0.88	1.32	0.452
Employed no access to money	1.33	1.08	1.64	0.007
Benefits but coping	1.44	1.20	1.74	<0.001
Most deprived	1.52	1.24	1.87	<0.001
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.08	0.90	1.29	0.4
Ethnicity				
White	1.22	1.06	1.40	0.005
Mixed	1.15	0.89	1.48	0.3
Asian	1.00 (reference)			
Black	0.76	0.48	1.22	0.3
Other	0.43	0.21	0.88	0.02

Number of observations: 13,172. Imputations: 25. Average Relative Variance Increased (RVI) = 0.040; Largest Fraction of Missing Information (FMI) = 0.195

5.4.1.4. Stratified analysis by ethnicity: developmental disorders from medical records

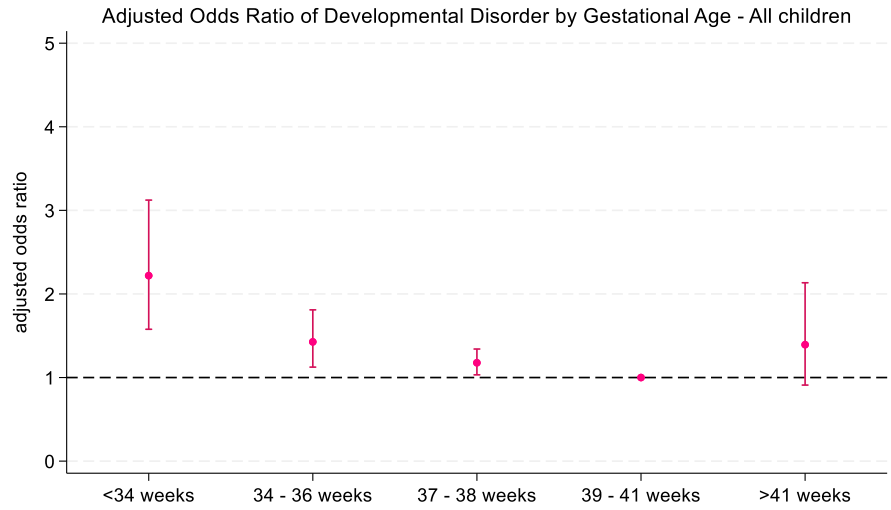
The relationship between gestational age and odds of developmental disorder were similar in the stratified analysis (see Table 58). In the analysis of White children, none of the odds ratios for gestational age remained statistically significant. Complete case analysis and imputation diagnostics are shown in appendices 5.19 and 5.20.

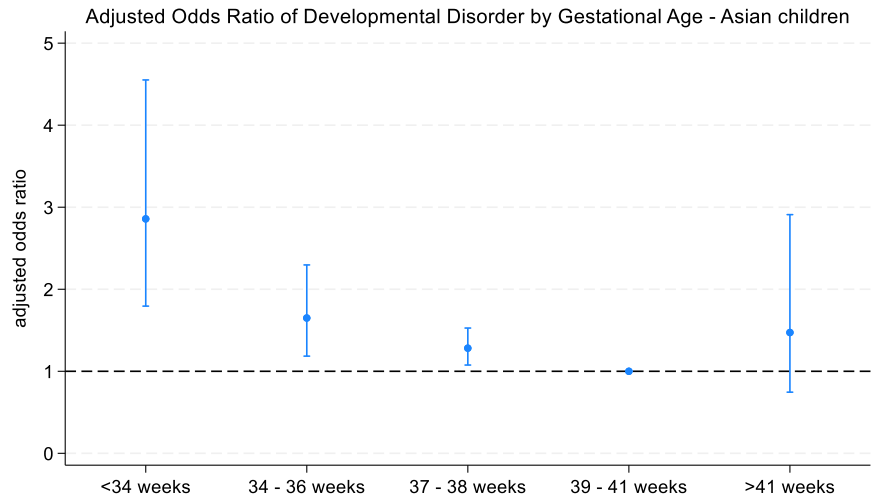
Table 58 - Odds ratio of developmental disorder by gestational age. Stratified analysis, imputed dataset.

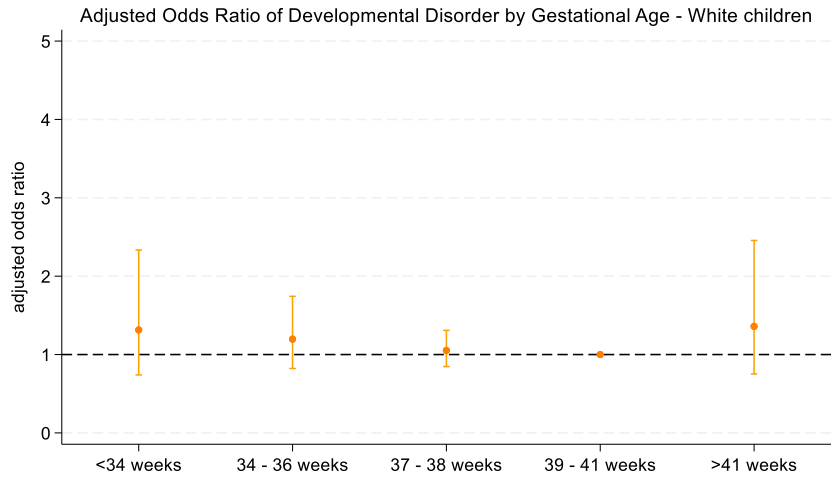
	Asian children				White Children			
	n = 6,970				n = 5,001			
	Odds ratio	**95% conf. interval**		**P value**	**Odds ratio**	**95% conf. interval**		**P value**
Gestational age								
<34 weeks	2.86	1.79	4.55	<0.0001	1.31	0.74	2.33	0.4
34 - 36 weeks	1.65	1.18	2.3	0.003	1.20	0.82	1.74	0.3
37 - 38 weeks	1.28	1.08	1.53	0.005	1.05	0.85	1.31	0.6
39 – 41 weeks	1 (reference)							
>41 weeks	1.47	0.75	2.91	0.3	1.36	0.75	2.46	0.3
Child's sex								
Female	1 (reference)							
Male	1.82	1.55	2.12	<0.0001	2.43	2.02	2.91	<0.0001
Small for gestational age (SGA)								
Not SGA	1 (reference)							
SGA	1.29	1.07	1.57	0.008	1.11	0.83	1.48	0.5
Maternal age at delivery (years)								
<21	1.17	0.82	1.67	0.4	0.91	0.66	1.26	0.6
21-25	1.06	0.84	1.33	0.6	1.11	0.84	1.46	0.4
26-30	1.05	0.85	1.31	0.6	1.03	0.78	1.35	0.9
31-35	1 (reference)							
>35	1.43	1.08	1.9	0.01	1.42	1.02	1.98	0.04
Socio-economic position								
Most educated, least deprived	1 (reference)							
Employed not materially deprived	1.29	0.94	1.78	0.1	1.23	0.89	1.7	0.2
Employed no access to money	1.2	0.9	1.6	0.2	1.65	1.17	2.34	0.005
Benefits but coping	1.22	0.97	1.54	0.09	2.12	1.48	3.04	<0.0001
Most deprived	1.09	0.8	1.49	0.6	2.3	1.62	3.28	<0.0001
Maternal smoking in pregnancy								
Non-smoking	1 (reference)							
Smoking (any)	1.15	0.73	1.82	0.5	1.02	0.82	1.28	0.8

Asian children: Imputations: 22; Average Relative Variance Increased (RVI): 0.06; Largest Fraction of Missing Information (FMI):0.25; White children Average RVI: 0.05; Largest FMI:0.20. Note these are two separate models.

Figure 89 - Coefficient plots showing odds ratios and 95% confidence intervals of any developmental disorder, adjusted for sex, small for gestational age, maternal age, socio-economic position and ethnicity, using imputed datasets. Bottom two graphs are separate models, stratified by ethnicity







5.4.1.5 Sensitivity analysis – restricted case ascertainment strategy definition

The imputed multivariable regression model was repeated, but using the restricted case ascertainment strategy, as described in chapter 3 and chapter 4. The effect sizes are similar as in the main model, although slightly larger see Table 59, e.g. odds ratio of developmental disorder <34 weeks in restricted model 2.41 (95% CI 1.67 to 3.47) vs. 2.22 (95% CI 1.58 to 3.12) in main model. Therefore, this restricted case ascertainment strategy was not used further.

Table 59 - Restricted definition of developmental disorder. Imputed dataset.

N = 13,172. Imputations: 25; Average Relative Variance Increased (RVI): 0.049; Largest Fraction of Missing Information (FMI):0.18. Imputations: 18.

	Odds ratio	95% confidence interval		P value
Gestational age				
<34 weeks	2.41	1.67	3.47	<0.001
34 - 36 weeks	1.46	1.12	1.90	0.005
37 - 38 weeks	1.26	1.09	1.46	0.001
39-41 weeks	1 (reference)			
>41 weeks	1.54	0.97	2.43	0.07
Child's sex				
Female	1 (reference)			
Male	2.27	1.99	2.58	<0.001
Small for gestational age (SGA)				
not SGA	1 (reference)			
SGA	1.29	1.09	1.53	0.003
Maternal age at delivery (years)				
<21	1.03	0.81	1.32	0.8
21-25	1.08	0.90	1.30	0.4
26-30	1.09	0.91	1.30	0.4
31-35	1 (reference)			
>35	1.41	1.13	1.78	0.003
Socio-economic position				
Most educated, least deprived	1 (reference)			
Employed not materially deprived	21.10	0.88	1.41	0.4
Employed no access to money	1.31	1.03	1.66	0.03
Benefits but coping	1.45	1.18	1.78	<0.001
Most deprived	1.48	1.17	1.87	0.001
Maternal smoking in pregnancy				
Non-smoking				
Smoking (any)	1.02	0.84	1.25	0.8
Ethnicity				
White	1.22	1.05	1.42	0.01
Mixed	1.22	0.93	1.61	0.1
Asian	1 (reference)			
Black	0.73	0.43	1.25	0.3
Other	0.35	0.14	0.85	0.02

5.4.2. Modelling the relationship between gestational age and the cumulative incidence of Special Educational Needs and Disability (SEND)

The development of the model, including comparison with complete case analysis, and model diagnostics are shown in appendix 5.13. The results are similar to the unadjusted model (Table 113); the effect of gestational age persists in the adjusted model (see Table 60).

The final adjusted imputed model – SEND

Table 60 - Odds ratio of Special Educational Needs and Disability by gestation. Imputed model

	Odds ratio	95% confidence interval		P value
Gestational age				
<34 weeks	2.10	1.52	2.90	<0.001
34 - 36 weeks	1.60	1.32	1.94	<0.001
37 - 38 weeks	1.14	1.02	1.26	0.02
39-41 weeks	1.00 (reference)			
>41 weeks	1.14	0.79	1.66	0.5
Child's sex				
Male	2.20	2.02	2.41	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.33	1.18	1.50	<0.001
Maternal age (in years) at child's delivery				
<21	1.20	1.02	1.43	0.03
21-25	1.12	0.99	1.28	0.08
26-30	1.08	0.95	1.23	0.2
31-35	1.00 (reference)			
>35	1.12	0.95	1.33	0.2
Socio-economic position				
Least deprived	1.00 (reference)			
Employed not mat deprived	1.02	0.87	1.20	0.808
Employed no access to money	1.43	1.20	1.70	<0.001
Benefits but coping	2.01	1.73	2.33	<0.001
Most deprived	2.51	2.13	2.96	<0.001
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.07	0.93	1.23	0.3
Ethnicity				
White	1.24	1.11	1.38	<0.001
Mixed	1.00	0.82	1.22	1.0
Asian	1.00 (reference)			
Black	1.07	0.74	1.55	0.7
Other	0.51	0.31	0.83	0.006

Number of observations: 11,492 Imputations: 25. Average Relative Variance Increased (RVI) = 0.055; Largest Fraction of Missing Information (FMI) = 0.163. The category with the lowest incidence of developmental disorder was used as the reference for each variable

Stratified analysis by ethnicity: Special Educational Needs and Disabilities from education records

In the analysis of White children, none of the odds ratios remained statistically significant, except for SEND in the 34-36 week group (Table 61 and Figure 90).

Table 61 - Stratified analysis, imputed dataset. Special Educational Needs and Disabilities

	Asian children				White Children			
	n = 6,314				n = 4,198			
	Odds ratio	95% conf. interval		P value	Odds ratio	95% conf. interval		P value
Gestational age								
<34 weeks	2.92	1.87	4.55	<0.0001	1.35	0.81	2.26	0.3
34 - 36 weeks	1.57	1.19	2.06	0.001	1.72	1.27	2.35	0.001
37 - 38 weeks	1.18	1.03	1.35	0.01	1.05	0.88	1.26	0.6
39 – 41 weeks	1 (reference)							
>41 weeks	1.08	0.61	1.91	0.8	1.35	0.79	2.29	0.3
Child's sex								
Female	1 (reference)							
Male	2.07	1.84	2.33	<0.0001	2.41	2.09	2.79	<0.0001
Small for gestational age (SGA)								
Not SGA	1 (reference)							
SGA	1.31	1.13	1.52	<0.0001	1.23	0.97	1.56	0.09
Maternal age at delivery (years)								
<21	1.43	1.1	1.87	0.008	1.1	0.85	1.43	0.5
21-25	1.16	0.98	1.38	0.08	1.05	0.84	1.32	0.7
26-30	1.14	0.97	1.34	0.1	1	0.8	1.25	0.99
31-35	1 (reference)							
>35	1.08	0.86	1.36	0.5	1.3	0.98	1.73	0.07
Socio-economic position								
Most educated, least deprived	1 (reference)							
Employed not materially deprived	1.05	0.8	1.39	0.7	1.13	0.87	1.46	0.4
Employed no access to money	1.4	1.11	1.76	0.005	1.55	1.16	2.07	0.003
Benefits but coping	1.9	1.57	2.29	<0.0001	2.49	1.81	3.43	<0.0001
Most deprived	2.2	1.77	2.74	<0.0001	3.01	2.25	4.04	<0.0001
Maternal smoking in pregnancy								
Non-smoking	1 (reference)							
Smoking (any)	0.91	0.64	1.29	0.6	1.08	0.9	1.28	0.4

Asian children : Imputations: 23; RVI: 0.074; FMI: 0.23. White children: Imputations: 19, Average RVI: 0.07, Largest FMI: 0.25. Note these are two separate models.

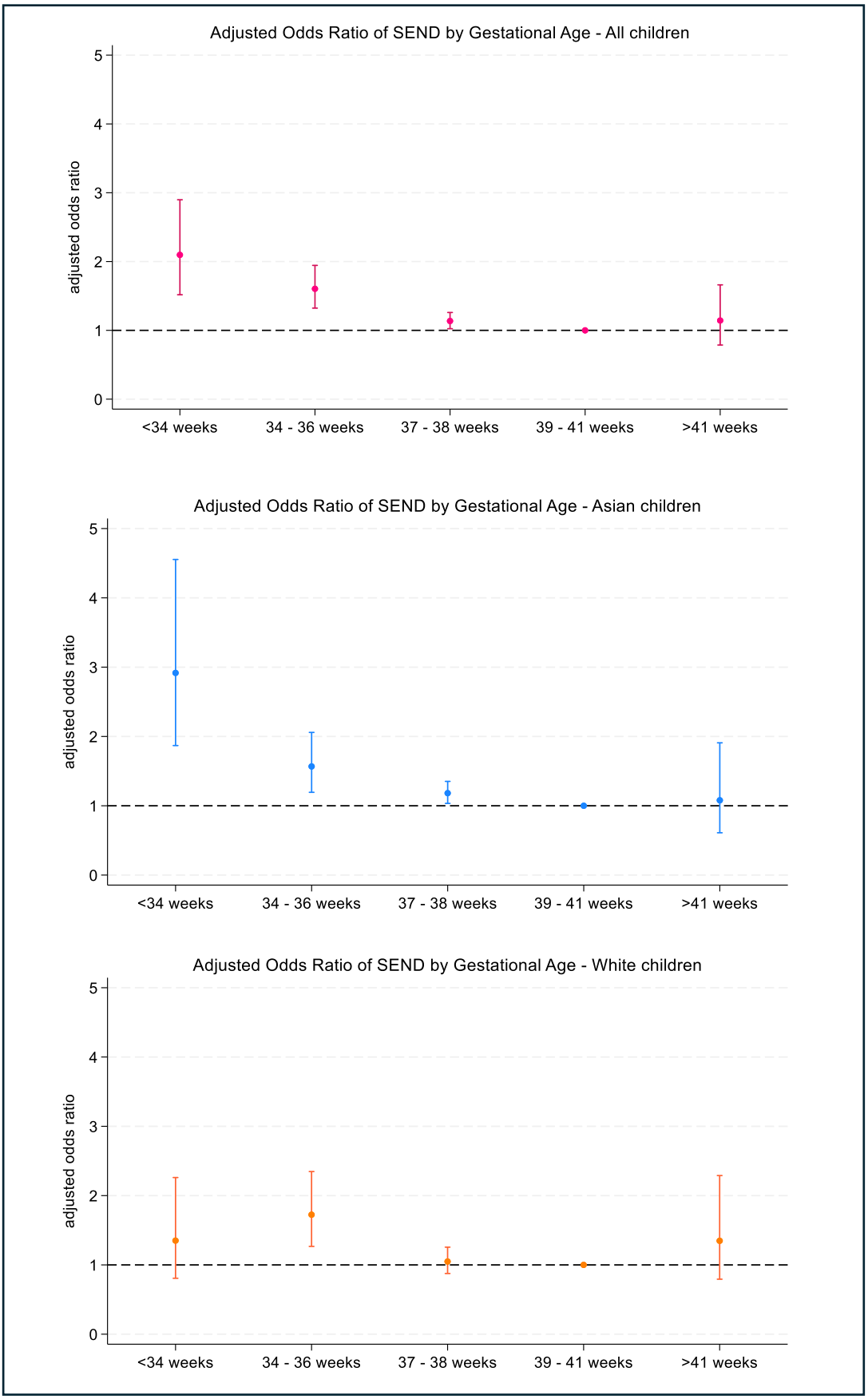


Figure 90 - Coefficient plots showing odds ratios and 95% confidence intervals of SEND, adjusted for sex, small for gestational age, maternal age, socio-economic position and ethnicity, using imputed datasets. Bottom two graphs are separate models, stratified by ethnicity

5.5. Discussion

5.5.1 Key findings

The results presented in this chapter corresponded to thesis objectives 4 and 5.

4. To explore how the cumulative incidence and incidence rate of developmental disorders are associated with neonatal, antenatal, and sociodemographic factors, including ethnicity
5. To investigate how the cumulative incidence of developmental disorders varies according to gestational age using regression models

Univariable analysis

Neonatal characteristics:

- Gestational age: For both developmental disorder from medical records and SEND from education records, the lowest cumulative incidence and incidence rate was in the full term (39-41 weeks) group, and the highest incidence was in the <34 week group. There was a clearer association with gestational age for some disorders (such as CP and developmental delay) than there was with other disorders (e.g. ASD and ADHD)
- Child's sex: developmental disorders and SEND were more common amongst boys compared to girls
- Small for gestational age (SGA): developmental disorders and SEND were more common amongst children born SGA

Antenatal characteristics:

- Maternal age: developmental disorders and SEND were least common amongst children whose mothers were 31-35 years old when they were delivered. Developmental disorders were most common in older mothers (>35 at delivery), whereas SEND was most common in younger mothers (<21 at delivery)
- Gestational diabetes and pre-eclampsia: the cumulative incidence of developmental disorders and SEND were slightly higher where either of these conditions had been present, but this was not statistically significant.

Socio-demographic characteristics and breastfeeding:

- Socio-economic position: developmental disorders and SEND were most common amongst the most deprived group.
- Child's ethnicity: The cumulative incidence of developmental disorders and SEND were highest among White children.
- Consanguinity: The cumulative incidence of developmental disorders and SEND were higher if mothers were related to fathers, apart from by marriage.
- Mother drank alcohol during pregnancy: The cumulative incidence of SEND was higher if mothers consumed alcohol in the first 3 months of pregnancy. No other statistically significant relationships with alcohol consumption and either outcome was demonstrated.
- Mother smoked during pregnancy: developmental disorders and SEND were more common if there was a history of smoking in pregnancy.
- Developmental disorders and SEND were less common amongst children who had ever been breastfed.

Ethnicity, deprivation and gestational age

- The relationship between socio-economic position and cumulative incidence of developmental disorders was different according to children's ethnicity. Among White children the cumulative incidence of developmental disorder increased with increasing deprivation. In the Asian group the cumulative incidence of developmental disorder was relatively unchanged with socio-economic position. Like with developmental disorders, the cumulative incidences of SEND were similar for White and Asian children in the "least deprived most educated" group, but then they diverged as deprivation increased (although in the case of SEND the patterns are similar). The cumulative incidence doubled in the White children from the least to most deprived, whereas in the Asian children the increase from the least deprived to most deprived was not as large.

Adjusted analysis

- When adjusting for covariates the association between gestational age and developmental disorder and SEND persisted.

- There were increased odds of developmental disorder from medical records and SEND from education records in all gestational age groups born before full term, with relationships persisting after adjusting for covariates
    - The odds ratio for developmental disorder and SEND was highest in the <34 week group; 2.22 (95% CI 1.58 to 3.12) and 2.10 (95% CI 1.52 to 2.90) respectively.
    - The effect sizes reduced with increasing gestational age, up to full term, and were statistically significant even in the early term groups, for both outcomes.
- The odds ratios for both outcomes then increased in the post term group, but this was not statistically significant.
- Multivariable analysis of the association between gestational age and individual developmental disorder was not possible due to small numbers of cases.

Ethnicity, deprivation and gestational age

- The relationship between gestational age and odds of developmental disorder and SEND were similar in the analysis stratified by ethnicity, compared to the main multivariable regression analysis. All effect sizes stayed the same or were larger and remained statistically significant in the analysis of only Asian children. In the analysis of White children, none of the odds ratios remained statistically significant, except for SEND in the 34-36 week group .

5.5.2. Strengths and Limitations

Covariates

Not all of the variables within the conceptual framework could be investigated in the analyses, and others could not be incorporated into the multivariable analysis due to multi-collinearity, for various reasons, discussed below.

Neonatal illness

This could not be investigated thoroughly with the available data. Initially admission to special care was considered as a proxy marker for neonatal illness, but this was problematic for two reasons: 20 children < 32 weeks were recorded as “not admitted to special care”, thus, the quality of the variable was questionable. An alternative approach would have been to look for clinical codes in the children’s secondary care records that related to neonatal illness, but this option was not considered until after the data had been requested, and it would have added substantial complexity.

Small for gestational age

Small for gestational age was defined as being below the 10th centile for weight according to gestational age, using population centiles. However, since SGA is known to vary by ethnicity National guidelines recommend the use of 'customised' growth charts which include ethnicity. (Gardosi et al., 2018; Norris et al., 2015; Kelly et al., 2009; Kierans et al., 2008). The clinicians in Bradford chose not to adopt this practice, as it was felt that the lower birth weight seen in Asian babies may be the result of lower SEP and a resultant suboptimal intrauterine environment, i.e. it is not necessarily normal physiology related to ethnic difference (Norris et al., 2015). This is important when considering the generalisability of these findings, as many other maternity units in the UK will be using customised growth charts.

Socio-economic position

Socio-economic position was measured once, during pregnancy. It is possible that a families' socio-economic position could have changed during a child's early years. The 5 group LCA was chosen as the most useful measure of SEP within. However, using this variable does limit straightforward generalisability. A sensitivity analysis was carried out using means tested benefits and maternal education as an alternative measure of SEP. These are also not ideal, since there is variable missingness in the MTB variable by ethnicity (14.7% vs 18.3% missing for White and Asian mothers respectively). Using this alternative measure of SEP the estimates did not change substantially (see appendix 5.11 and 5.17).

Ethnicity

Aggregating ethnic groups was not ideal, for example, for the '*ethnicity_5*' variable BiB combines Indian, Pakistani, Bangladeshi, Chinese and 'Any other Asian background" into "Asian", which may be of limited value. With the exception of the Asian and White groups, the remaining ethnic groups were too small to investigate thoroughly. Even in the stratified analysis of White children the confidence intervals of the effect sizes widened to encompass the null value of 1, likely because of the limited sample size.

Maternal mental health

Maternal mental health was a covariate of interest. However, it was not included in the regression modelling. Maternal anxiety and depression seemed to be associated with the child's gestational age. For example, of the women who had minimal anxiety symptoms, 69.1% of babies had been born full term, and 3.9% had been late preterm. For the women with severe anxiety symptoms 65.1% were born at full term, and 5.9% were born late preterm.

These results were similar for maternal depression: of women with no significant symptoms of depression 69.4% had had babies born at full term, 3.9% were born late preterm, but for the women with moderately severe or severe depression only 66.0% were born at full term, and a larger proportion (relatively) had been born late preterm (6.6%). However, it was decided not to investigate these variables any further, since these were data collected later on, in the "Growing Up" survey when the BiB children were aged 6-10 years. Interpreting how this could be related to the evolution of a developmental disorder was not possible: since the median age for the first code was as late as 11 years for some conditions (see Table 47) it could have been that the worse mental health in these mothers was a result of the increased likelihood of their children having a developmental disorder; whilst a developmental disorder is not synonymous with a disability, caring for a disabled child has been shown to be associated with worse mental health in mothers (Masefield et al., 2022). It is also important to consider in this cohort, that women from different ethnic background may have different presentations when in psychological distress; women from minoritised ethnic groups have been shown to be less likely to access treatment compared to White British women despite being more likely to be identified as having anxiety (Prady, Pickett, Gilbody et al., 2016). Furthermore, these variables were highly missing (>50%). Data on maternal mental health were collected during pregnancy, but this was also highly missing (>30%), and the missingness was associated with ethnicity (see appendix 5.21), potentially introducing a source of bias, therefore this variable was not investigated further either.

Breastfeeding

Breastfeeding could not be included in the regression modelling. An 'Ever breastfed" variable was created using data from the AllIn, MEDALL and BiB1000 sub cohorts (See Figure 58). These cohorts combined contained data on 3,867 children within the analysis cohort, which meant the variable was missing for 70.7% of the analysis cohort. Therefore, it was not included in the regression modelling. An alternative approach which was evaluated, was to use clinical codes within the mother's notes related to breastfeeding. However, this was felt to be unreliable, as the absence of a code relating to breastfeeding would not have necessarily meant the child had not been breastfed. The binary nature of 'ever breast fed" was also felt to be of limited clinical value, since there is a likely a difference between having had a single breastfeed within the first week, compared to exclusive breastmilk for a year.

Health data - completeness

BiB did not have access to child developmental clinic records, which is where many diagnoses for developmental disorders such as ASD are initially made. The secondary care records were all inpatient stays; the outpatient data appeared incomplete, as the only ICD-10 code which matched the list sent to BiB was “Presbycusis, right ear”, which was a code was later excluded as it was not related to developmental hearing impairment.

Bradford Royal infirmary does not have all tertiary paediatric services, for example paediatrics intensive care. It is possible that some children have attended another hospital to receive care, and there is no way of determining this. This would have led to had an underestimation of the disease burden.

Health data – coding

The accuracy of the coding in participants' medical records is a prerequisite for this investigation. However, as with all studies using linked routine health data, these data are mainly used for clinical purposes, other studies have shown that the quality of coding within primary care records can vary according to the presence (or absence) of financial or safety incentives (Bradley, Lawrence and Carder, 2018; Khan, Harrison and Rose, 2010b).

The case ascertainment strategy was intentionally broad, including not only codes related to the diagnosis of developmental disorders, but also the signs and symptoms of developmental disorders, to account for known variation in how people with different ethnicities access healthcare, as well as to mitigate for unusual coding practices (Prady et al., 2016). Despite their inclusion in the NICE guideline for the developmental follow-up of children born preterm, some conditions that are listed here as "developmental disorders" do not meet the more stringent definition of the term. A sensitivity analysis was carried out, to determine if the effects were similar when excluding sleep apnoea, and only using diagnostic clinical codes. Whilst the cumulative incidence was lower using the restricted case ascertainment strategy, the effect sizes were only marginally different.

Using routine health data, it is not possible to definitively determine whether a child genuinely does not have a condition, or if the condition is simply not coded in their records. For example, this thesis has confirmed that Asian children in the BiB cohort are less likely to have a code related to ASD than White children. It has been proposed that this is related to structural inequalities in healthcare pathways (N8 Research Partnership, 2024), but it could also be related to cultural factors, or genetics.

Missing data

Missing data resulted in the exclusion of some covariates from the multivariable analyses. Missing data can lead to biased estimates and can reduce the power to find an effect (Sterne, White, Carlin et al., 2009). Due to the pre-stated inclusion and exclusion criteria, there were no missing data for exposure or primary outcome (although, as discussed there may have been some children seen in secondary care outside of Bradford whose records are not available).

For the multivariable regression analyses missing data within covariates was managed using multiple imputation chained equations (MICE) under the assumption that data was MAR, which was clinically plausible. Auxiliary variables were included in the imputation, to improve the imputation of the variables to be included in the multivariable model, reduce bias, and also to make more plausible the assumption that the data is MAR, as described in the methods (Azur et al., 2011; White et al., 2011). The number of imputations exceeded the proportion of missing data as recommended, providing the FMI is ≤0.5 as in this case (White et al., 2011; Von Hippel, 2009). The imputed variables were compared to the complete variables and there were not substantial differences. If this had not been the case a sensitivity analysis could have been undertaken (Little and Rubin, 2019), however, it was decided that the approach used was appropriate. There is no definitive test to determine the mechanism of missing data and there remains a possibility that data was not MAR (Azur et al., 2011).

Model diagnostics

Model diagnostics suggested there was no problematic collinearity in the final models. Further diagnostic tests were carried out on the complete case analysis, because goodness-of-fit tests are not directly applicable to multiple imputation results (StataCorp, nd.). Using optimal probability cut offs, the developmental disorder model and SEND model would correctly classify 59.6% and 61.3 % of children respectively. Receiver operating characteristic curve showed an area under the curve (AUC) of 0.64 and 0.66 for developmental disorders and SEND respectively. An AUC of 1 indicates a perfect test; 0.5 is no better than random (Hand, 2010). This suggests the models have reasonable discrimination. Hosmer-Lemeshow goodness-of-fit test showed a $\chi 2 = 4.33$ and 5.04, with p-values = 0.8 and 0.8 for the developmental disorders model and the SEND model respectively, indicating no evidence of lack of fit for both models (Hosmer and Lemesbow, 1980). Influential outliers and covariate patterns were investigated, and the model was rerun without potentially significant outlying patterns; there were no covariate patterns which exerted undue influence on the estimates.

5.5.3. Chapter summary

This chapter has described how the cumulative incidence and incidence rate of developmental disorders, in medical records, and SEND in education records, are associated with neonatal, antenatal, and sociodemographic factors, both using univariable and multivariable analysis. The multivariable analysis was adjusted for important covariates, and both complete case analysis as well as results from an imputed dataset were presented.

Multivariable models have shown that even when controlling for important covariates there is increased odds of developmental disorder and SEND when born before full term, which remains evident in the early term (37-38 week) group. The models were largely unchanged when using imputed or complete case analysis. Stratified analysis showed that the relationship between gestational age and developmental disorder was similar in Asian children.

The following chapter builds on these results, by presenting the results of a latent class analysis describing the profiles of developmental disorders within the cohort.

Chapter 6: Results 3 - Profiles of Developmental Disorders

6.1. Introduction

The results presented in this chapter correspond to the sixth and seventh objectives of the thesis as follows:

6. To carry out a latent class analysis to identify profiles of developmental outcomes
7. To determine which factors are associated with different profiles of developmental disorders

Exploring patterns of co-occurrence of developmental disorder may help clinicians, educational professionals, and academics to have a clearer picture of children, and their families', experiences, beyond a single diagnosis. Children's health and development may be affected differently by particular combinations of disorders and there could be ramifications for children's services designed to diagnose and manage developmental disorders.

These results are based on the analysis cohort whose selection was described in Chapter 3 - methods, and Chapter 4 – Results 1. These results are based only on medical records (i.e., not education records), as the education records did not contain information on the children's specific types of SEND. The latent class analysis included the developmental disorders as per NICE plus a category of developmental disorders which was not classifiable further, and data from 13,172 children. It included data from children who died, and children who withdrew, up until the point of withdrawal. The approximated 12th birthday was used as a cut-off, so any incident codes beyond that point were not counted.

6.2. Model assessment and selection

The lowest Bayesian information criterion (BIC) and sample-size adjusted Bayesian information criterion (aBIC) were in the four class model, the lowest AIC in the five class model, and the lowest cAIC in the three class model, where lower values are preferable (see Table 62 and Figure 91). Relative entropy was very similar across the classes, and joint highest in the three and four class models.

Table 62 - Model fit indices for Latent Class analysis models with 1 to 5 classes

Class	LL	likelihood -ratio	AIC	BIC	cAIC	aBIC	relative entropy
1	-13177.8	5540.1	26383.7	26488.5	26502.5	26444	NA
2	-11067.7	1319.7	22193.3	22410.4	22439.4	22318.3	0.939
3	-10887.6	959.5	21863.1	22192.5	22236.5	22052.7	0.953
4	-10815.0	814.4	21748.0	22189.7	22248.7	22002.2	0.953
5	-10788.2	760.3	21723.9	22278.4	22352.4	22043.2	0.931

LL = log-likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; cAIC = consistent Akaike information criterion; aBIC = sample-size adjusted BIC; AWE = approximate weight of evidence criterion

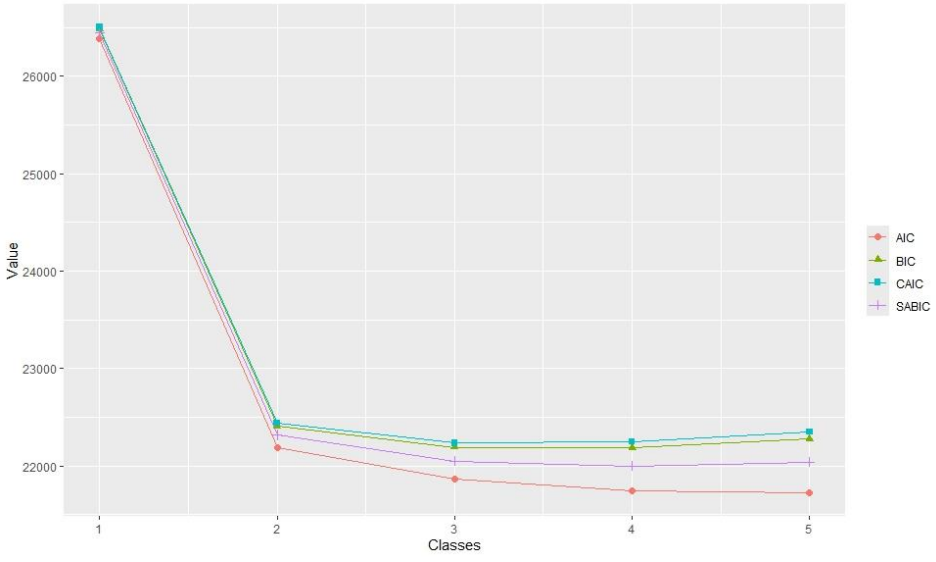


Figure 91 - Elbow plot

AIC: Akaike information criterion; BIC: Bayesian information criterion; cAIC: consistent Akaike information criterion; aBIC: sample-size adjusted BIC

The average posterior probability (measuring how accurately class membership is predicted) is shown for the three class and four class models (Table 63). An average posterior probability of >0.7 is acceptable; the higher the value the more accurately class membership is predicted (Nylund-Gibson and Choi, 2018).

Table 63 - Average posterior probabilities for three and four class models

3 class model				
Group	1	2	3	
Average posterior probability	0.99	0.87	0.87	
4 class model				
Group	1	2	3	4
Average posterior probability	0.99	0.75	0.89	0.87

The three class and four class models were assessed and compared using profile plots, see Figure 92 and Figure 110- appendix 6.1. The four class model was chosen as it was the model with the lowest BIC (which has been demonstrated to be the most reliable fit statistic (Weller et al., 2020)) and the most useful in a clinical context; the key difference between the three and four class models was the separation out of children with primary educational problems from children with primarily ASD and social, emotional, and behavioural problems.

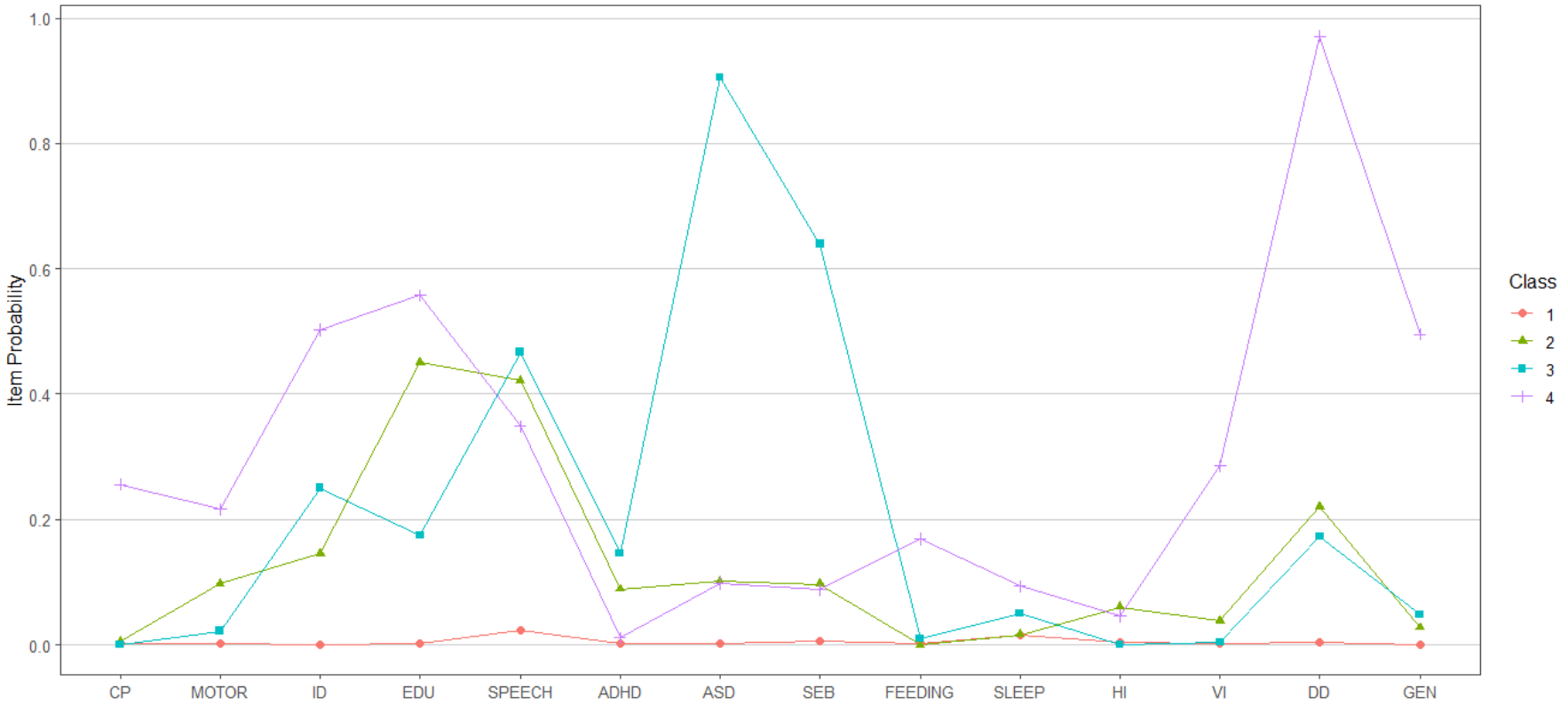


Figure 92 – Profile plot: final latent class analysis model

CP: Cerebral palsy; MOTOR: motor function problems; ID: Learning disability/Intellectual disability; EDU: Education problem; SPEECH: Speech, language and communication disorders; ADHD: Hyperactivity, impulsivity, and inattention, including Attention Deficit Hyperactivity Disorder (ADHD); ASD: Autism spectrum disorder; SEB: Social, emotional, and behavioural problems; FEEDING: feeding problems; SLEEP: sleep apnoea; HI: hearing impairment; VI: visual impairment; DD: developmental delay; GEN: general developmental disorder. (N = 13,172).NB, There were no codes in participants' records corresponding to Executive function problems.

6.3. Four class solution: description

Table 64 - Results for the Latent Class Analysis (4-class solution). Probability of each developmental disorder by latent class

	Full sample	**Class 1 – "Typical development"**	**Class 2 – "Educational difficulties"**	**Class 3 – "Social, emotional, behavioural & communication difficulties"**	**Class 4 – "Early developmental impairment, with physical & intellectual disabilities"**
Number of children	13,172	12,536	347	189	100
Average posterior probabilities	N/A	0.99	0.75	0.89	0.87
Cerebral palsy (CP)	0.33%	0.11%	0.59%	0.00%	25.57%
Motor function problem	0.69%	0.17%	9.80%	2.20%	21.61%
Intellectual disability	1.28%	0.00%	14.50%	24.98%	50.22%
Education problem	2.46%	0.29%	45.06%	17.44%	55.74%
Speech, language, and communication disorders	4.55%	2.29%	42.11%	46.70%	34.84%
ADHD	0.74%	0.23%	8.88%	14.56%	1.09%
ASD	2.08%	0.23%	10.15%	90.50%	9.80%
Social, emotional, and behavioural problems	2.04%	0.67%	9.69%	63.95%	8.75%
Feeding problems	0.38%	0.24%	0.00%	0.95%	16.91%
Sleep apnoea	1.66%	1.53%	1.61%	5.01%	9.33%
Hearing impairment	0.59%	0.38%	6.04%	0.00%	4.64%
Visual impairment	0.62%	0.27%	3.84%	0.37%	28.52%
Developmental delay	2.08%	0.31%	22.07%	17.26%	97.09%
General/unclassifiable developmental disorder	0.64%	0.06%	2.74%	4.80%	49.56%

ASD: Autism Spectrum Disorder. ADHD: Attention deficit Hyperactivity Disorder. Total sample: 13,172

The probability of a child within each class having a particular developmental disorder is shown in Table 64. The classes are described below:

Class 1 "Typical Development": This was the largest group, containing 12,536 children. Children in this class had low chance of any developmental disorders. There was a 2.3% probability of a speech, language, and communication disorder and a 1.5% probability of sleep apnoea. There was <1% probability of any other developmental disorders.

Class 2 "Educational Difficulties": Children in this class often had specific educational problems (45%) such as dyslexia and dyscalculia, but compared to the other atypical development groups, there was a relatively low probability (14.5%) of learning/intellectual disability. This group also had a relatively high (6.0%, vs. 0.6% in the full sample) probability of hearing impairment.

Class 3 "Social, emotional, behavioural and communication difficulties": There was a high (90.5%) probability of ASD in this group, as well as social, emotional, and behavioural problems (64.0%). This was also the group with the highest likelihood of ADHD (14.6%), and speech, language, and communication disorders (46.7%). There was a 25.0% probability of learning/intellectual disability.

Class 4 "Early developmental impairment, with physical and intellectual disabilities": The smallest group, with only 100 children. This group was the most likely to have cerebral palsy (25.6%), learning/intellectual disability (50.2%), motor function problems (21.6%), feeding problems (16.9%) and sleep apnoea (9.3%). There was a 97.1% probability of early developmental impairment (also known as 'developmental delay').

6.4. Cohort characteristics by class membership

The clinical and socio-demographic characteristics of the children varied within each class (see appendix 6.2). Compared to class 1 "Typical development" there was a higher proportion of boys in all other classes, especially class 3 "Social, emotional, behavioural and communication difficulties" (84.1% male). 20% of the children in group 2 "Educational difficulties" and 23% of the children in class 4 "Early developmental impairment, with physical and intellectual disabilities" were SGA, compared to 14% of the whole cohort who were SGA. The proportion of children from each socio-economic position group varied less in class 3 than in all the other groups. The distribution of maternal age and multiplicity did not vary by latent class.

6.5. Adjusted multinomial regression to predict class membership

Multinomial regression was carried out to explore the associations between gestational age and latent class membership, whilst controlling for the same covariates as in the previous chapter. Four covariates (small for gestational age, maternal smoking, socio-economic position, and ethnicity) had missing values and were imputed using multiple imputation by chained equations, the completed proportions were very similar to the observed (see appendix 6.4). For comparison a complete case analysis of the adjusted multinomial regression is shown in appendix 6.3.

Table 65 and Figure 93 show the adjusted relative risk ratio of latent class membership according to gestational age, compared to class 1- "Typical development". All gestational age groups less than full term were found to be associated with increased risk of membership of Class 2 "Educational problems". There appears to be an association with gestational age in class 4 "Early developmental impairment, with physical and intellectual disabilities", although this was only statistically significant in the <34 weeks group. Note there are only 100 children in this class. There does not appear to be an association between gestational age and membership of class 3 "Social, emotional, behavioural and communication difficulties".

Table 65 –Multivariable multinomial logistic regression using imputed dataset

Class 1 – "Typical development" is reference class. RRR = relative risk ratio. CI = confidence intervals. 25 imputations were carried out. Pre-eclampsia, gestational diabetes, consanguinity, and maternal parity were included in the imputation as auxiliary variables. Largest Relative Variance Increased (RVI) = 0.05, Largest Fraction of Missing Information (FMI) = 0.26

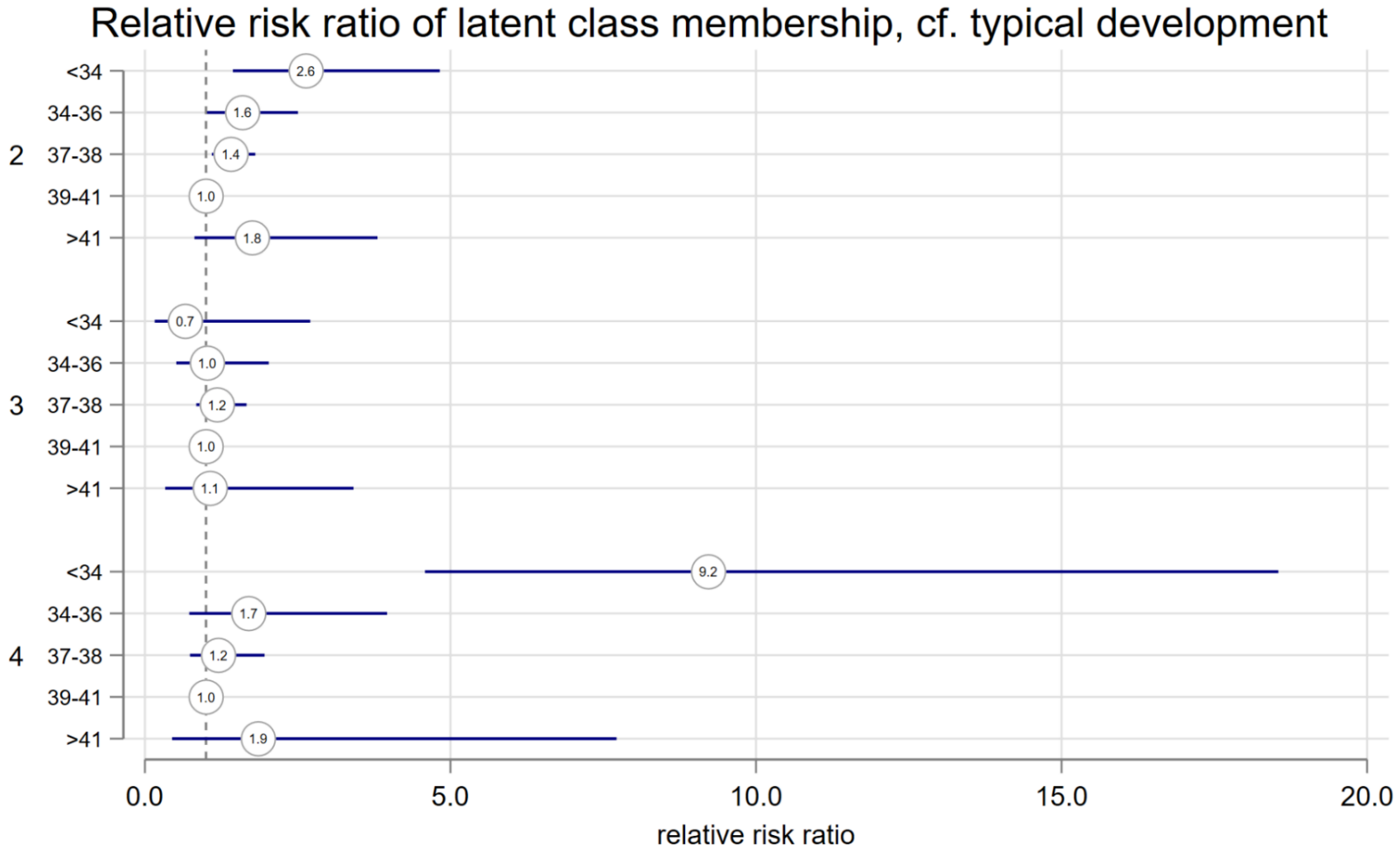
	RRR	**95% CI**		**P value**	**RRR**	**95% CI**		**P value**	**RRR**	**95% CI**		**P value**
	Group 2 – "Educational difficulties", n = 347				**Group 3 – "Social, emotional, behavioural & communication difficulties", n = 189**				**Group 4 – "Early developmental impairment, with physical & intellectual disabilities", n = 100**			
Gestational age categories (weeks)												
<34	2.64	1.44	4.83	0.002	0.66	0.16	2.71	0.6	9.22	4.58	18.55	<0.0001
34-36	1.60	1.02	2.5	0.04	1.02	0.51	2.03	0.96	1.70	0.73	3.96	0.2
37-38	1.41	1.1	1.81	0.007	1.18	0.84	1.66	0.3	1.20	0.74	1.96	0.5
39-41	1.00 (ref)				1.00 (ref)				1.00 (ref)			
>41	1.76	0.81	3.81	0.2	1.07	0.33	3.41	0.9	1.85	0.45	7.72	0.4
Child's sex												
female	1.00 (ref)				1.00 (ref)				1.00 (ref)			
male	1.78	1.42	2.22	<0.0001	5.09	3.44	7.54	<0.0001	1.63	1.09	2.45	0.02
Small for gestational age (SGA)												
SGA	1.6	1.21	2.11	0.001	0.86	0.53	1.38	0.5	1.76	1.09	2.85	0.02
Not SGA	1.00 (ref)				1.00 (ref)				1.00 (ref)			
Maternal age (years)												
<21	0.80	0.50	1.25	0.3	1.55	0.87	2.79	0.1	1.36	0.62	2.96	0.4
21-25	0.99	0.72	1.37	0.96	1.33	0.83	2.16	0.2	1.07	0.59	1.94	0.8
26-30	1.04	0.76	1.43	0.8	1.39	0.88	2.2	0.2	1.02	0.57	1.82	0.9
31-35	1.00 (ref)				1.00 (ref)				1.00 (ref)			
>35	1.32	0.89	1.97	0.2	1.97	1.14	3.38	0.01	1.08	0.5	2.36	0.8
Socio-economic position												
Least deprived and most educated	1.00 (ref)				1.00 (ref)				1.00 (ref)			
Employed, not materially deprived	1.21	0.77	1.88	0.4	0.88	0.52	1.47	0.6	0.73	0.27	1.99	0.5
Employed, no access to money	1.28	0.8	2.04	0.3	0.99	0.59	1.66	0.96	2.36	1.11	5.00	0.03
Benefits not materially deprived	2.08	1.42	3.04	<0.0001	0.64	0.39	1.06	0.09	2.12	1.04	4.31	0.04

	RRR	95% CI		P value	RRR	95% CI		P value	RRR	95% CI		P value
	Group 2 – "Educational difficulties", n = 347				**Group 3 – "Social, emotional, behavioural & communication difficulties", n = 189**				**Group 4 – "Early developmental impairment, with physical & intellectual disabilities", n = 100**			
Most economically deprived	2.2	1.44	3.37	<0.0001	0.84	0.48	1.48	0.5	2.12	0.95	4.72	0.07
Maternal smoking in pregnancy (any)												
no smoking	1.00 (ref)				1.00 (ref)				1.00 (ref)			
smoking	0.91	0.62	1.33	0.6	1.15	0.74	1.78	0.5	0.32	0.12	0.85	0.02
Ethnicity												
White	1.00 (ref)				1.00 (ref)				1.00 (ref)			
Mixed	0.48	0.25	0.93	0.03	1.37	0.82	2.29	0.2	1.43	0.53	3.82	0.5
Asian	0.84	0.64	1.1	0.2	0.62	0.43	0.89	0.009	1.51	0.88	2.6	0.1
Black	0.84	0.36	1.94	0.7	0.90	0.32	2.51	0.8	0.67	0.09	5.09	0.7
Other	0.21	0.03	1.51	0.1	0.60	0.15	2.5	0.5	0	0	.	0.99

N = 13,172.

Figure 93 - Coefficient plot show adjusted relative risk ratio of latent class membership according to gestational age, compared to class 1 "Typical Development"

Imputed dataset. Adjusted for child's sex, small for gestational age, maternal age, maternal smoking, socio-economic position, and ethnicity.



6.6. Discussion

The results presented in this chapter correspond to the sixth and seventh objectives of the thesis as follows:

6. To carry out a latent class analysis to identify profiles of developmental outcomes
7. To determine which factors are associated with different profiles of developmental disorders

6.6.1. Key findings

Within the Born in Bradford analysis cohort there were four distinct profiles of developmental disorders identified by the latent class analysis, which from largest to smallest were: "Typical Development", "Educational Difficulties", "Social, emotional, behavioural, and communication difficulties", and "Early developmental impairment, with physical and intellectual disabilities". The majority of children had 'Typical development' and were unlikely to have any diagnosed developmental disorders, apart from a small (2.3%) probability of speech, language, and communication disorder.

The adjusted multinomial regression showed an increased relative risk of membership of the "Educational difficulties" group, compared to the "Typical development" group in all gestational age groups less than full term. There was also an increased relative risk of membership of the "Early developmental impairment, with physical and intellectual disabilities" group, compared to "Typical development" in all gestational age groups less than full term, although this was only statistically significant in the <34 weeks gestation group where the adjusted RRR compared to "Typical development" was 9.22 (95% confidence intervals: 4.58 to 18.55).

There did not appear to be any association between gestational age and membership of Group 3 "Social, emotional, behavioural, and communication difficulties". It is possible that ASD, and ADHD which frequently co-occurs with ASD, are not as strongly associated with gestational age as other developmental disorders. Parenting, as well as other environmental factors, are known to influence children's social, emotional, and behavioural development (Franke, Keown and Sanders, 2020); these may be stronger influences than gestational age compared to the disorders clustered in the other profiles. Genetics could also play a more important role, especially when we consider that ASD and ADHD have a heritability of 50% and 74% respectively (Faraone and Larsson, 2019; Baio, Wiggins, Christensen et al., 2018). Furthermore,

boys are known to be more likely than girls to be diagnosed with ASD and ADHD, (Pinares-Garcia, Stratikopoulos, Zagato et al., 2018) as is demonstrated in this research; in the typical development group 50.7% were male, whereas in group 3 "Social, emotional, behavioural, and communication difficulties" 84.1% were male. Groups 2 and 4 were 64.3% and 62.0% male respectively; whilst male sex predisposes to all groups of developmental disorders, the association is particularly clear in group 3 "Social, emotional, behavioural, and communication difficulties" and may eclipse the importance of gestational immaturity.

6.6.2. Strengths and limitations

The latent class analysis was the first of its kind using UK data, including a full range of developmental disorders and the full range of gestational ages. This study has strengths over previous studies using latent class analysis to explore profiles of developmental disorders in children born before full term; previous studies have not used a full range of developmental disorders, have relied solely on parent reported measures, have been limited by short follow-up times, or have only investigated a specific gestational age group (Camerota, McGowan, Aschner et al., 2024; Twilhaar, Pierrat, Marchand-Martin et al., 2022; Johnson, Waheed, Manktelow et al., 2018). For example, Johnson *et al.* identified three classes of development within their moderate-late preterm group: "optimal development" and "non-optimal development" with high risk for behavioural problems and delayed social–emotional competence, as well as a third class with features similar to the very preterm phenotype, characterised by cognitive and language delays. The study was limited by its reliance on parent reported measures rather than clinical assessments and a short follow-up period (2 years). Given that developmental disorders are often diagnosed much later than this (e.g. ASD at 3 ½ years (van 't Hof et al., 2021) and ADHD at 7 years (Centers for Disease Control and Prevention (CDC), 2013)), the use of assessment solely at age 2 is limited. Following children up into school age allows a more thorough assessment of a range of outcomes.

These analyses do not rule out the possibility of diagnostic overshadowing, where symptoms are ascribed to one diagnosis while another co-existing disorder is overlooked (Jamieson & Mason, 2019). Diagnostic overshadowing is particularly challenging in developmental disorders; as previously discussed and demonstrated, there can be significant overlap in presentation and occurrence. For example, in the "Education difficulties" group there was a 45.1% probability of a code related to an education problem, and a 42.1% probability of a code related to a speech, language or communication disorder. Developmental language disorder

(DLD), a type of speech, language or communication need where there is no identified medical cause, such as hearing loss, or structural neurological damage (Abbott & Love 2023; Bishop et al. 2017), may be under recognised by both education and healthcare professionals, as it has a subtle presentation and is known to co-occur with other developmental disorders (Bishop et al. 2017; McGregor, 2020). Children with speech, language and communication disorders such as DLD may require tailored interventions, often involving collaboration between families, speech and language therapists, and teaching staff (Ebbels et al. 2019). This will require the initial recognition of the speech, language or communication disorder, which, when it occurs in conjunction with other developmental problems, may not happen. The potential for diagnostic overshadowing is concerning, not least because it may lead to children not receiving appropriate support and management, with potential longer term implications for their development and outcomes.

As with all the research in this thesis using routine health data, this study relies upon the accuracy of the coding within the participants' medical records. The case ascertainment strategy was broad, to account for unusual coding practices as well as previously described differences in how people with different ethnicities access healthcare (Prady et al., 2016).

Aside from the "Typical development" class, the remaining profiles all contained less than 5% of the analysis cohort. Previously, this was thought to be problematic, however, recent LCA research methodology suggests that whether the class "makes conceptual sense" is more important than numerical 'rules' (Weller et al., 2020).

6.6.3. Chapter summary

The latent class analysis has revealed four distinct profiles of co-existence of developmental disorders. Two of the classes of developmental disorder were associated with birth before full term: there was an increased adjusted relative risk ratio of "Educational difficulties" for all groups born before full term. The effect of gestational age was larger in group 4 "Early developmental impairment, with physical and intellectual disabilities" but only statistically significant in the very/moderately preterm group

The following (final) chapter will discuss the results of the preceding three results chapters, in the context of the results of the systematic review and wider literature.

Chapter 7: Discussion

This chapter is a discussion of the findings presented in this thesis, together with its implications, both in terms of research and practice. As stated in Chapter 1: Background, the aims of this thesis were as follows:

- To investigate the prevalence and risk of developmental disorders in children born before full term compared to those born at full term
- To determine the cumulative incidence and incidence rates of developmental disorders according to gestational age
- To explore profiles of developmental disorders
- To examine which factors, particularly ethnicity, are associated with the incidence and profiles of developmental disorder

These aims were designed to address a gap in the existing literature: the majority of research to date either focused on extremely preterm babies, who make up a small minority of all births before full term, or had short follow up periods, or only focused on a single outcome measure. Most existing literature was based on cohort studies in which most participants were White, which was problematic since in many developed countries (including the UK) women from minoritised ethnic groups have higher risk of preterm birth.

The ultimate goal was to enable provision of accurate, personalised counselling to families about the developmental risks their children might face, to contribute to evidence which could inform obstetric decision making, and to assist with service planning.

7.1. Summary of key findings

The systematic review has shown that there is an inverse relationship between gestational age and risk and prevalence of most developmental disorders. The cumulative incidence of developmental disorders in the Born in Bradford cohort, by the age of 12, was 11.4% (95% CI 10.8 to 11.9%) in medical records. As in the systematic review, the overall incidence of any developmental disorder was related to gestational age, with the lowest incidence being in the 39-41 week group, and the highest incidence being amongst children born <34 weeks. This persisted after adjusting for covariates and was demonstrated in all gestational age groups

born before full term, including the early term (37-38 weeks) born children. Stratified adjusted analyses showed the effect of gestational age persisted amongst Asian children.

The cumulative incidence of developmental disorder varied with child's sex (higher incidence in boys), maternal age at delivery (lowest incidence in 31-35 years), SGA (higher incidence if SGA), consanguinity (higher incidence if consanguineous parents), maternal smoking (higher incidence if smoked), and breastfeeding (lower incidence if ever breastfed). In White children the cumulative incidence of developmental disorders increased with increasing deprivation, but in Asian children the cumulative incidence of developmental disorder was relatively unchanged with socio-economic position. Overall, the incidence of developmental disorders was lower amongst Asian children compared to White children. This was largely driven by lower incidence rates of ASD, ADHD, and social, emotional, and behavioural problems seen in Asian children. Compared to White children, Asian children had a higher incidence of rarer conditions (hearing impairment and learning disability).

Within the Born in Bradford cohort there were four profiles of developmental disorder: The majority of children had "typical development" and were unlikely to have any diagnosed developmental disorders. The remaining 4.8% of the cohort fell into one of three classes: "Educational difficulties", "Social, emotional, behavioural and communication difficulties", and "Early developmental impairment, with physical and intellectual disabilities". There was an increased relative risk of membership of the "Educational difficulties" group, compared to the "Typical development" group in all gestational age groups less than full term. Whilst there was an increased relative risk of membership of the "Early developmental impairment, with physical and intellectual disabilities" group, compared to "Typical development" in all gestational age groups less than full term, this was only statistically significant in the <34 weeks gestation group. This suggests that the problems most likely to be experienced by children born late preterm and early term are educational difficulties not necessarily related to cognitive impairment.

Whilst the overall cumulative incidence of any developmental disorder by the age of 12 was 11.4% (95% CI 10.8 to 11.9%), only 4.8% of children fell into one of the non-typical development groups as identified by the LCA. This is because the LCA has shown that the majority of children who have a speech, language, or communication disorder have no other developmental disorders in their records and could therefore be said to have "Typical development".

7.2. Context and interpretation

Gestational age and developmental disorders

This research has shown the risk of developmental disorders associated with birth before full term extends to children born late preterm and early term. Given 'preterm pathologies' such as intraventricular haemorrhage and retinopathy of prematurity are rare in these gestational age groups, it had been suggested this could be a reflection of deprivation, since poverty is associated with both prematurity and impaired brain growth (Maalouf et al., 2021), or antenatal problems (such as pre-eclampsia and gestational diabetes), which also predispose to both prematurity and developmental disorder (Kugelman and Colin, 2013). However, multivariable modelling, adjusting for deprivation and SGA (as an indicator of fetal compromise secondary to antenatal pathology), suggests there is a true effect of immaturity. Likewise, two of the profiles of developmental disorder identified in the LCA were associated with birth before full term; there was an increased adjusted relative risk ratio of "Educational difficulties" for all gestational age groups born before full term. The effect of gestational age was larger in the "Early developmental impairment, with physical and intellectual disabilities" group but only statistically significant in the very/moderately preterm group, compared to "Typical development". These results are consistent with the systematic review findings, which showed that the most prevalent problem amongst the children born 32-38 weeks was low educational attainment. This likely reflects differences in the underlying pathophysiological processes; late preterm babies, whilst unlikely to have any major structural brain abnormalities such as IVH or PVL, may suffer from subtle changes in cerebral structure and neuronal connectivity as well as microstructural anomalies in white matter tracts (Pettinger et al., 2023; Kelly, Thompson, Spittle et al., 2020; Cheong, Thompson, Spittle et al., 2016; Kelly, Cheong, Gabra Fam et al., 2016; Walsh, Doyle, Anderson et al., 2014; Kugelman and Colin, 2013). The experience of the late preterm infant is therefore not simply "mild prematurity", rather it is a different process, reflected in the different profile of disorders they are likely to have.

Whilst the majority of evidence from the systematic review was based on outcomes measured in early childhood, there was some evidence that the increased risk of developmental disorders associated with birth before full term persists through childhood, in contrast to other research suggesting developmental delay in preterm infants may be transient (Patel, 2016; Schmidt, 2012). Evidence using Millennium Cohort Study (MCS) data, published after the data collection for the systematic review, showed that whilst late preterm children were less likely to achieve the expected level in English and Mathematics at the end of primary school, by the end of secondary school this effect was no longer evident when using a binary measure of

passing at least five General Certificate of Secondary Education examinations including English and Mathematics (Alterman et al., 2022). Avon Longitudinal Study of Parents and Children (ALSPAC) data (which was not included in the systematic review as preterm birth was dichotomised into <37 weeks and >37 weeks) showed that the disparity in educational outcomes of children born preterm compared to term born children became less evident with age, but the increased odds of SEND persisted up to age 16 (Odd, Evans and Emond, 2016).

MCS data has also been used to explore the underlying reasons for the association between early term delivery and SEND. The authors found an adjusted risk ratio of SEND for early term born children, compared to full term children, of 1.33 (95% CI 1.11 to 1.59). In a second analysis the cohort was restricted to only spontaneous onset deliveries (i.e. excluding inductions or planned caesareans). The risks were similar in this subset (adjusted risk ratio 1.34 (95% CI 1.11 to 1.61)), which the authors felt implied that gestational immaturity was the primary driver for the increased risk of SEND in early term children, as opposed to being related to being a proxy marker of fetal or maternal problems resulting in iatrogenic early delivery (Alterman et al., 2021). Unfortunately, it was not possible to replicate this investigation in the BiB cohort; instead, SGA was used as a measure of intrauterine compromise.

Profiles of developmental disorder and gestational age

Latent class analyses have been used previously to explore outcomes of children born before full term. However, they have not used a full range of gestational ages, as used in this thesis, and have not explored a full range of developmental disorders and have measured outcomes at younger ages. Johnson et al. assessed a moderate-to-late preterm (n = 1,139) and a term cohort (n = 1,255) at two years of age. They identified three classes of development in the moderate-to-late preterm children: “optimal development”, “non-optimal development” (behavioural problems and delayed social–emotional competence), and “very preterm” development (cognitive and language delays) (Johnson et al., 2018). Since two separate cohorts with different gestational ages were used comparison with the BiB results is challenging.

Camerota et al. used latent profile analysis to explore the developmental outcomes of two year old children who were born very preterm (n = 2,036). Four profiles of cognitive, motor, and behavioural characteristics were identified. Approximately 85% of children had low probability of developmental delay or behavioural problems (Camerota et al., 2024). In

comparison in the <34 week group in BiB, 95.2% of the children were categorised in the "Typical development" profile. Twilhaar et al. also explored outcomes amongst very preterm children from the EPIPAGE-2 study (n = 1,977) using latent profile analysis, at 5 years of age. They also identified four profiles: no deficit in any domain (45%); motor and cognitive deficits without behavioural/psychosocial deficits (31%); primarily behavioural and psychosocial deficits (16%); and deficits in multiple domains (8%). It appears the proportion of children experiencing typical development in this cohort is lower, than in Camerota et al. This might be because the outcomes were measured at 5 years of age, when there has been more time for difficulties to emerge. As with this thesis, the authors found male sex was associated with higher odds for all "suboptimal" profiles (Twilhaar et al., 2022).

Gestational age compared to other factors

Gestational age, specifically birth before full term, was the focus of this thesis. However, it is important to put the risk associated with birth before full term in the context of other risk factors. For example, male sex is strongly associated with developmental disorders and all profiles of non-typical development, as shown by the difference in cumulative incidence and by the multinomial regression following the latent class analysis (Table 65); the cumulative incidence of any developmental disorder amongst boys was 14.8%, amongst girls it was 7.7%, whereas the difference for late preterm birth was less pronounced: 14.7% of late preterm children had a developmental disorder, vs. 10.6% of full term children.

A Danish national cohort study including 1.3 million children showed that boys (compared to girls) had higher cumulative incidence of intellectual disability 1.52% (95% CI, 1.46 to 1.59%) vs. 0.88%, (95% CI, 0.85 to 0.92%), ASD 4.26% (95% CI, 4.16 to 4.36%) vs. 1.77% (95% CI, 1.72 to 1.82%), ADHD 5.90% (95% CI, 5.76 to 6.03%) vs. 3.04% (95% CI, 2.97 to 3.11%) (Dalsgaard, Thorsteinsson, Trabjerg et al., 2020).

Incidence of developmental disorder: comparison with other studies

Direct comparison with other sources is difficult; studies measure outcomes at different ages, use varied outcome definitions, or use different measures of disease burden. However, bearing this in mind, the cumulative incidence of developmental disorder in the Born in Bradford cohort appears high. Mitha *et al.* found an incidence rate for their composite outcome of epilepsy, motor, cognitive, visual, or hearing impairment ranged from 4.6/1,000 person years amongst the full term group, to 9.2/1,000 person years in the moderately preterm, and 6.5/1,000 person years in the late preterm group (Mitha, Chen, Razaz et al., 2024). The overall incidence rate of developmental disorders in the BiB cohort was 10.0 (95% CI 9.5 to 10.4) per 1,000 person years, i.e. higher than that observed by Mitha et al. However, this was a Swedish cohort, from a different epoch (born 1998 - 2012), who used a slightly different case ascertainment strategy, and did not include all developmental disorders (i.e., ASD and ADHD).

In England approximately 3-4% of children have a developmental disorder (Harris, 2017). There were 636 children in the BiB cohort (4.8%) who fell into one of the three non-typical latent classes. This figure may be more illuminating than the overall incidence rate or cumulative incidence of developmental disorder, since the LCA has shown that many children with a code relating to a speech, language and communication disorder have no other developmental disorders in their records. However, it is likely that the incidence of developmental disorders truly is higher in Bradford compared to other parts of the UK, and other comparable countries, given known association between poverty and developmental disorders, and the high levels of deprivation in Bradford (Cree, Bitsko, Robinson et al., 2016; Field, Boyle, Draper et al., 2016; Wong and Edwards, 2013; Wright et al., 2013). Similarly, the cumulative incidence of SEND appears high. In England and Wales in 2023/24, 18.4% of pupils received SEND support (including EHCPs); in BiB the prevalence of SEND peaks in year 6, at 20.5% (95% CI 19.8 to 21.3%). This fits with evidence that children who require SEND support are more likely to come from deprived homes; it has been proposed that deprivation is both a cause as well as a consequence of SEND (Shaw, Bernardes, Trethewey et al., 2016). Indeed, univariable analyses showed that the effect of deprivation was more pronounced for SEND in education records compared to developmental disorders in medical records (see Figure 86). In the systematic review the prevalence of SEND in term children was 7.1%, and 13.2% in late preterm children. This likely reflects differences in the definitions of SEND internationally.

The relationship between gestational age and developmental disorders was similar between the systematic review and the secondary data analysis using BiB. However, there were some differences, such as in the SR the prevalence of ASD was much lower than ADHD. This could

well reflect differences in case ascertainment and highlights one of the limitations of the systematic review: that the studies all used different means of defining their outcomes, which made meaningful combination of results challenging. Furthermore, there is substantial difference internationally between different background prevalence of individual developmental disorders (Global Research on Developmental Disabilities Collaborators, 2018).

Ethnicity, socio-economic position, and birth before full term

Preterm and early term birth are more common amongst minoritised ethnic groups nationally (Office for National Statistics, 2023) as well as in the BiB cohort, where a larger proportion of White babies (72.6%) were born at full term compared to Asian (68.1%), Black (69.0%), and babies with Mixed ethnic background (69.5%). Despite the known link between ethnicity and prematurity, there was very little pre-existing evidence regarding developmental disorders in association with gestational age amongst children from minoritised ethnic groups in the UK (Pettinger et al., 2023).

The reasons for the higher proportion of preterm and early term birth amongst minoritised ethnic groups is not certain**.** As the evidence regarding the risk (both short and long term, for both mother and baby) of early term birth has grown, interventions have been trialled to reduce the proportion of babies born early term. In the USA the proportion of early term deliveries has fallen from 30.2% to 24.4% between 2006 and 2014, as the number of elective deliveries before 39 weeks has been reduced (Richards, Kramer, Deb-Rinker et al., 2016b; Berrien, Devente, French et al., 2014; Oshiro, Kowalewski, Sappenfield et al., 2013). It is more challenging to reduce the number of medically indicated or spontaneous early-term deliveries (Oshiro et al., 2013). In many countries the proportion of babies born early term remains high; for example, in China the incidence of early term birth is 29.9% which is believed to be related to the universal two child policy (Zhang, Williams, Wang et al., 2021). Demonstrating that the proportion of babies born before full term is modifiable (either through quality improvement initiatives, or unintentionally following broader policy changes), and knowing that the proportion of babies born preterm varies with ethnicity, suggests caution should be applied when explaining a difference in outcome as purely the result of ethnic differences; differences in socio-economic position have been shown to partly explain differences in health outcomes including preterm birth (Li et al., 2019; Norris et al., 2015; Nazroo, 2003; Karlsen and Nazroo, 2002; Davey Smith, Neaton, Wentworth et al., 1998). Birth before full term is an adverse pregnancy outcome, and should not be normalised, in any ethnic group.

Ethnicity, socio-economic position, and developmental disorders

Although the stratified analysis showed the effects of birth before full term were evident amongst Asian children, the overall incidence (both cumulative incidence and incidence rate) of developmental disorder in BiB was higher amongst White compared to Asian children.

There is very little existing evidence about developmental disorders in children from minoritised ethnic groups in the UK who have been born preterm, so it is difficult to make direct comparisons; although the NICE guideline for the developmental follow up of children born preterm states that being from a "black, Asian or other minority ethnic group" is an independent risk factor for developmental delay (NICE, 2017b). The majority of studies exploring differences between ethnicities are from the USA, which has a different socio-economic and healthcare structure to the UK, although there was some signal from other countries that children from ethnic groups which are historically disadvantaged (i.e. those with non-European heritage) are more likely to have developmental disorders (Pettinger et al., 2023; Hanly et al., 2018).

The incidence rates of individual developmental disorders shown in chapter 4 demonstrated that the overall lower incidence of developmental disorders seen in Asian children was largely driven by lower incidence rates of ASD and social, emotional, and behavioural problems compared to White children, as well as lower rates of ADHD. When incidence rate is used as the measure of overall disease burden, as opposed to cumulative incidence, the difference in incidence is clearer (see Figure 96), because the data was not censored at age 12, and ASD, ADHD and social, emotional and behavioural problems had higher median ages at which the codes first appeared in the children's notes, compared to conditions which were more common in Asian children.

It is possible that these differences may reflect truly lower disease burden for some conditions in the Asian community. Genetic factors could be involved given that ASD and ADHD have a high heritability of 50% and 74% respectively (Faraone and Larsson, 2019; Baio et al., 2018). Conversely, it has been proposed that the lower incidence of ASD is a result of under-diagnosis related to structural inequalities in healthcare pathways (N8 Research Partnership, 2024).

The "Social, emotional, behavioural, and communication difficulties" group identified by the LCA was not associated with gestational age. These findings were in contrast to the ASD meta-analysis in the systematic review, which included 403,699 children from three studies, and found an association between ASD and gestational age, that was proportional to the degree of prematurity: 32-33 weeks: RR 1.75 (95% CI: 1.13-2.69), 34-36 weeks RR: 1.42 (95% CI: 1.08-

1.88), 37-38 weeks: 1.13 (95% CI: 0.98-1.29), compared to full term. The three studies included in the systematic review measured outcomes age 2, which is much younger than the median age of a code relating to ASD first appearing in a child's records in the BiB cohort, suggesting this is quite a different process. Also, the majority of the participants in the meta-analysis were from Canada, limiting the extent to which results can be compared directly. There was also a similar association between some social, emotional and behavioural disorders, and ADHD and gestational age in the systematic review. Whilst it is feasible that ASD and ADHD (which frequently co-occur) are not as strongly associated with gestational age as other developmental disorders, and other factors such as genetics, parenting, and sex may play a more important role, it seems likely that this result is at least in part related to the ethnic make-up of the BiB cohort, since Asian children are less likely than White children to receive a diagnosis of ASD (N8 Research Partnership, 2024).

Asian children were more likely than White children to have rarer conditions like hearing impairments and learning disabilities, which can have a major impact on a child's life; people with learning disabilities are more likely to experience severe physical and mental health problems as well as a shorter life expectancy (NICE, 2021). This result may be in part explained by the association between ethnicity and consanguinity, which has been shown here to be associated with increased risk of developmental disorders (Table 54), which is consistent with previous studies which have shown children whose parents are consanguineous are at increased risk of child mortality and developmental disorders (Small et al., 2024; Khan et al., 2010a).

Deprivation and Ethnicity

Both developmental disorders and SEND have higher cumulative incidence amongst more deprived children. However, the relationship with socio-economic position is different for White and Asian children; in the White group the cumulative incidence of developmental disorder increases with worsening deprivation (Figure 86). In the Asian group the cumulative incidence of developmental disorder is relatively unchanged with socio-economic position; the lowest incidence is in the least deprived and most educated group (9.4%), but the highest incidence (12.9%) is seen in the 'employed not materially deprived' group. These results point away from the argument of genetic difference, since there is very little difference between the incidence of developmental disorders between the White and Asian children when only the least deprived families are considered.

Considering SEND from education records, in the "least deprived most educated" group, the cumulative incidences for the two ethnic groups are very similar, but as deprivation rises, the cumulative incidence becomes more different, and the lines diverge. However, unlike developmental disorders in the medical records, the patterns are similar; for both ethnic groups, the risk of SEND increases with deprivation. Education services are arguably more universal and accessible to children than health services; all children should have regular contact with education services, whereas parents have to act as the first gatekeepers for healthcare, and their ability or desire to access medical advice may be influenced by social, economic or cultural factors, as discussed in chapter 1 (Lindquist et al., 2015; Dixon-Woods et al., 2006; Scheppers et al., 2006; Szczepura, 2005). Whilst the cumulative incidence of developmental disorders is statistically significantly lower in Asian children compared to White children, there is no statistically significant difference between the cumulative incidence or incidence rate of SEND for White and Asian children. This difference between health and education outcomes could point towards inequality in access to some services, or it could simply be another indication that the two outcome measures (developmental disorder in medical records and SEND in education records) are intrinsically dissimilar.

Developmental disorder from medical records and SEND from education records

Whilst the majority (73.1%) of children with a code corresponding to a developmental disorder in their medical records also received SEND support, many children (59.5%) who received SEND support did not have a developmental disorder coded in their medical records. In 2023, “Social, emotional, and mental health difficulties” were the second most common type of SEND need, after “speech, language, and communication difficulties” (see Figure 56); mental health difficulties were not one of the outcome measures in this thesis which may explain why so many children with SEND did not have a developmental disorder in their medical records. When EHCP was used as the outcome measure, instead of “any” SEND, only 0.2% of children with an EHCP did not also have a code related to developmental disorder in their medical records, perhaps indicating that these children not only have higher needs (as expected), but also a different profile of SEND.

The relationship between gestational age and SEND in educational records and developmental disorders in medical records were similar but not identical. This has not been researched previously. The effect of socio-economic position was more pronounced in the SEND model, and the effect of maternal age was different: the highest risk group in the developmental

disorder model was the >35 year old age group whereas in the SEND model it was the <21 age group, reflecting the differences underlying the labels of 'SEND' and 'developmental disorder'. Data from a Scottish cohort also showed that maternal age <20 was the highest risk group for SEND; compared to 25-29 years the unadjusted odds ratio of SEND was 1.37 (95% CI 1.30 to 1.45) (Mackay et al., 2010). Given these differences, research into the association between gestational age and SEND should not be automatically extrapolated to developmental disorders. This is important since the majority of UK research into outcomes of children born preterm has used educational data (either educational attainment or SEND) as its outcome measure (Alterman et al., 2022; Libuy et al., 2023; Alterman et al., 2021; Pettinger et al., 2020; Odd et al., 2019; Chan and Quigley, 2014; Odd et al., 2012; Quigley et al., 2012a; Mackay et al., 2010).

7.3. Clinical implications of the findings

7.3.1. Obstetrics

There is increased risk and prevalence of many developmental disorders when children are born before full term, and that risk extends to children born early term. As per national figures, Asian women in the BiB cohort are more likely than White women to give birth before full term. The stratified analysis of Asian children reveals that, despite being common, preterm delivery is still linked to a higher risk of developmental disorders and SEND. Furthermore, whilst the proportion of children affected by a developmental disorder is *generally* lower amongst children born between 32-38 weeks compared to extremely preterm children, late preterm and early term birth are more common than extremely preterm birth so small increases in relative risk (compared to full term children) may have a considerable impact both clinically and economically at a population level (Woythaler, 2019; Blencowe, Lee, Cousens et al., 2013; Kugelman and Colin, 2013). Therefore, if there is not a compelling indication for early term delivery, it should be avoided, irrespective of a woman's ethnicity.

7.3.2. Neonatology

Parents can be empowered by clinicians with information about the risks facing their children, but it remains unclear when or how this information should be delivered. For parents of children born late preterm it may be helpful to discuss with them the profiles of risk their children are most likely to experience. Late preterm children are more likely to have difficulties in school, compared to physical or intellectual disabilities, as a result of their immaturity. When providing guidance to parents on the possibility of developmental disorders, it is crucial to keep in mind that although birth before full term is linked to developmental disorders, the majority of children in the BiB cohort exhibit typical development, according to the latent class analysis.

7.3.3. Enhanced follow-up

The LCA showed that for children born <34 weeks, the aRRR for membership of Group 4 "Early developmental impairment, with physical and intellectual disabilities" was 9.22 (95% CI: 4.58 to 18.55). Moderately/very preterm children should be monitored for these disorders, and would benefit from visual screening and physiotherapy assessment for motor disorders including CP. This will be part of routine care for children born <30 weeks, who have

developmental follow-up to 2 years, or in some cases to 4 years of age (NICE, 2017b). An expansion of routine follow-up would need to be balanced against cost and time implications. A pragmatic approach might be to target children with additive risk factors (e.g. preterm, SGA, and male), or to use screening questionnaires such as the Parent Report of Children's Abilities-Revised (PARCA-R). Health visitors (specialist community public health nurses) would be ideally placed to act on concerns regarding children's development, however the service is already overstretched (Seaman, 2023).

7.3.4. General practice and community paediatrics

Clinical and socio-demographic factors can be used to help predict children's developmental profiles and assess risk of developmental disorders. Being aware of these factors could facilitate earlier diagnosis and intervention.

Knowledge of the local context is important when planning services, in order to meet the needs of the community. Within the BiB cohort overall, the developmental disorders with the highest incidence rates were speech, language, and communication disorders, ASD, and social, emotional, and behavioural problems. The unadjusted incidence rates of some developmental disorders varied with ethnicity; compared to White children, Asian children had higher rates of learning disabilities and hearing impairment but lower rates of attention deficit hyperactivity disorder and autism spectrum disorder.

Understanding how disorders co-occur might assist community paediatricians or GPs to anticipate a child's needs. For instance, the LCA showed that in the "Social, emotional, behavioural, and communication difficulties" group there was a 90.5% probability of ASD, there was also a 64.0% probability of social, emotional and behavioural problems, 46.7% probability of a speech, language and communication disorder (unsurprising as ASD is defined in part by difficulty with communication (Baron-Cohen and Lombardo, 2017)) and was the group with the highest probability (14.6%) of ADHD. In Group 4 "Early developmental impairment, with physical and intellectual disabilities" there was a 50.2% probability of an intellectual disability, 25.6% probability of CP and 28.5% probability of visual impairment. Group 2, "Educational Difficulties" were most likely (45%) to have educational problems, but they also had a relatively high (6.0%, vs. 0.6% in the full sample) probability of hearing impairment; children who have educational difficulties in school may benefit from additional hearing tests.

The group with the highest (46.7%) probability of a speech, language and communication disorder was group 3 “Social, emotional, behavioural, and communication difficulties”. However, there were only 189 children in group 3. In the “Typical development” group there was a 2.3% probability of a speech, language and communication disorder but since there were 12,536 children in this group, it is likely that the majority of children presenting with a speech, language and communication disorder go on to experience typical development. Clinicians need to discern between types of speech, language and communication disorder, in particular lack of communicative intent, as distinct from a speech impediment, in order to help discern between children who will go on to develop typically, compared with those who may have more complex journeys ahead.

7.3.5. Education

The systematic review found that the most prevalent developmental disorders amongst the children born 32-38 weeks were low educational attainment, across all age ranges (early years, primary school, and secondary school). In addition, membership of group 2 “Educational difficulties” was associated with all gestational age groups born before full term and was the largest class of children with non-typical development.

These results reinforce the need for better health and education service integration (Pettinger et al., 2020); teaching staff who are aware of the challenges related to prematurity may be able to detect issues and refer children to specialised care when needed; however other studies have shown that teachers feel ill equipped to do this at present and would like more training (Mitha, Chen, Altman et al., 2021; Johnson, Gilmore, Gallimore et al., 2015b).

Parents should be encouraged to inform schools if their child was born before full term, including early term. The LCA showed that children born late preterm and early term are more likely to experience specific problems such as dyscalculia and dyslexia than intellectual disability, which would require a different form of educational support.

7.4. Implications for future research

Evidence gaps were identified during the systematic review: there were several disorders where there were no data for early term children, or early term children were included within the studies' term reference category; there was no evidence available regarding feeding problems; there was very limited evidence regarding children from the UK from minoritised ethnic groups; there was little evidence related to longer term outcomes.

Some of these evidence gaps were addressed in the secondary data analysis, although more research involving children from minoritised ethnic backgrounds remains important; the majority of the Asian population from Bradford is from one specific region in Pakistan (Mirpur) (Wright et al., 2013) and therefore caution should be applied when considering if these results can be extrapolated to other British Asian populations. Replicating these methods in a population with a large community from a different minoritised ethnic group to see if the results are similar would be helpful.

The cumulative incidence of developmental disorders was lower in Asian children compared to White children. It is impossible to tell from these data whether this is a result of under recording or under diagnosis among Asian children, or if this is a 'real' result. Actively testing for developmental disorders would potentially overcome this, but this would be a huge undertaking, given the range of disorders considered and the sample size required. An alternative approach would be to explore variations in coding of developmental disorders by primary care practitioners, as this is known to vary based on funding incentives and on patients' ethnicity in other conditions (Bradley et al., 2018; Prady et al., 2016; Khan et al., 2010b).

Children born before full term were the focus of this thesis. However, the secondary data analysis has shown that there is an increased risk of developmental disorders and SEND in children born post term, as well as being more likely to be in class 3 "Educational difficulties" or class 4 "Early developmental impairment, with physical and intellectual disabilities" compared to "Typical development", although this does not reach statistical significance. There were very few children born post term in the BiB cohort, as women are usually offered induction if they go "overdue" due to the risk of stillbirth, neonatal morbidity, hypoxic ischaemic encephalopathy and resultant CP (Frank, Garfinkle, Oskoui et al., 2017; Linder, Hiersch, Fridman et al., 2017). However, there seemed to be an association between post maturity and conditions such as speech, language and communication disorders, developmental delay, and education problems. The mechanism for this is uncertain, and it

would be very interesting to investigate this further in a cohort with more post term deliveries. This would be useful for clinicians and parents when making informed choices about timing of delivery.

The study offers a snapshot of developmental disorders, which may not fully represent children's developmental trajectories. Using longitudinal data to monitor the evolution of developmental problems across time may have advantages. Born in Bradford is continuing to follow this cohort; subsequent research exploring outcomes at age 16 or 18 may offer a more complete picture of their developmental outcomes.

Finally, qualitative studies exploring parents experiences of the diagnostic journey would help interpret some the results which have been observed so far. A study exploring how best to deliver information to parents would be useful, since we rely at present on parents to act as gatekeepers to healthcare for their children when they are not under regular follow-up. It is feasible that parents may want to receive different amounts and types of information and at different times. A study designed to describe the experiences of parents of very preterm children, particularly in regard to their development and how this has impacted their families, suggested that a universal approach, or an approach where as much information as is available is delivered, might not be desirable:

"They didn't talk about [his developmental outcome] at all in the neonatal unit… You don't want to be thinking about in two years, three years' time, what's going to happen."

"many times, I've thought I wish I didn't have that information, it's best not to know, because I'm always on the lookout for something and … we could have maybe had a less stressful time. I know that's a bit burying you're head in the sands [sic] but it would have been nice not to have had it always in my head." (Harvey, Redshaw and Edwards, 2020)

7.5. Strengths and limitations

Various decisions about the methods and analyses required to meet the thesis aims and objectives were made, with resultant strengths and weaknesses. These are discussed below, first related to the systematic review, then the secondary data analysis.

7.5.1. Systematic review

Strengths

This systematic review is the first to explore the full range of developmental disorders in children born 32-38 weeks. It was a wide-ranging review with a comprehensive search strategy. This made it possible to locate and include all pertinent research. There was a total of over 8 million children included in the meta-analyses. Using multiple meta-analyses enabled comparison between different disorders, and also meant more meaningful combinations of outcomes could be made. Calculating prevalence of a full range of developmental disorders meant the increased relative risk associated with gestational age could be contextualised and prevalence of different developmental disorders across gestational ages could be compared.

Limitations

The review only included papers written in English, and the majority were from economically developed countries which could restrict the findings' applicability to other parts of the world. The review was also limited by the available primary studies; although there were a large number of children in total in the review, because each developmental disorder was considered separately according to gestational age subgroups, there were sometimes small numbers in each subgroup. The children in the studies were assessed at different ages; making meaningful combination of studies' results more difficult, since different conditions are more common at different ages. Term comparator groups were very variable, for example ≥ 37 weeks, >37 weeks, ≥39 weeks, 39-41 weeks, or 40 weeks. Whilst it would have been preferable to have a homogenous term comparator group, only including studies which used a *full* term (39-40/41 weeks) comparison group would have resulted in a substantial loss of data. The biggest challenge was the variety of diagnostic and screening tools used to measure outcomes. This was partly addressed by carrying out multiple different meta-analyses to try to ensure that the combinations were reasonable. However, it is still important to acknowledge that whilst some studies used diagnostic codes in medical records to determine their outcome, many studies used questionnaires, tests, and tools which were not developed to make formal diagnoses, but rather were intended as screeners.

7.5.2 Secondary data analysis

Strengths

The studies in this thesis using BiB data represent the most comprehensive studies of a full range of developmental disorders amongst a majority Asian population in the UK to date.

Many studies investigating the outcomes of children born preterm have had short follow-up times (Pettinger et al., 2023). This limits which disorders can be explored; in BiB the median age at which clinical codes first appeared in children's notes was often much later, for example, ADHD at 11 years. The BiB participants were aged 11-16 at the point of data extract, so this enabled a more thorough investigation of a full range of developmental disorders. This allowed comparisons between incidence rates of disorders to be made, including split by ethnicity, which helped interpret the findings. It also allowed exploration of the co-occurrence of developmental disorders in the LCA.

Using a full term comparison group (39-41 weeks) allowed the early term group to be investigated. Including early term children within the "term" comparison group (as many other studies have done) could reduce the effect size when investigating the effect of prematurity.

The case ascertainment strategy was intentionally broad, including not only codes related to the diagnosis of developmental disorders, but also the signs and symptoms of developmental disorders, to account for differences in how ethnic groups access healthcare as well as to mitigate for unusual coding practices (Prady et al., 2016). It is possible that some children detected by this strategy may not have gone on to receive a diagnosis of a developmental disorder. However, a sensitivity analysis showed that the relationship with gestational age in multivariable modelling using a restricted case ascertainment strategy was similar to the main model, and so this restricted case ascertainment strategy was not used further.

Limitations

Some specific challenges e.g. with statistical modelling are discussed at the end of the relevant results chapters. The broader limitations of the studies are described here.

The BiB cohort was chosen because it has a high proportion of Asian children, who have been historically under researched in the UK. However, the results of the secondary data analyses cannot be easily compared to those of other research due to some of the features of the BiB cohort and its design, in particular, the unique socio-demographic make-up of the cohort, for example, 66.7% of the analysis cohort lived in the most deprived postcodes nationally,

according to IMD quintiles, as well as the relatively low proportion of children born preterm, as discussed below.

The majority of the BiB cohort is bi-ethnic (Asian and White). The remaining ethnic groups were not large enough to investigate thoroughly. Even in the second largest ethnic group, White children, in the stratified multivariable analyses the confidence intervals of the effect sizes widened to encompass the null value of 1, likely because of the limited sample size. Using the 16 ethnic groups available from BiB would have led to very small groups. However, generalising ethnicity is problematic; there is a risk that a wide variety of people who otherwise differ substantially are incorrectly assumed to be homogeneous (Nazroo, Williams, Marmot et al., 2006). The *'ethnicity_5'* variable in BiB combines Indian, Pakistani, Bangladeshi, Chinese and 'Any other Asian background" into "Asian", which may be of limited value, although office for national statistics (ONS) data shows that Chinese, Indian, Bangladeshi and Pakistani heritage children all had higher average progress 8 scores (aged 16) than the national average, thus their combination, as per ONS, may not be unreasonable (Office for National Statistics, 2020).

There was a lower proportion of White children and higher proportion of Asian children in the education subset compared to the whole cohort. In addition, the proportion of children from the "least deprived and most educated" socio-economic group was lower in the education subset compared to the whole cohort. This suggests that White children, and children from the least deprived and most educated families, were more likely to move out of the area before the children started school, or go to private school, or be sent to schools out of area. This could be a source of selection bias.

Whilst the majority (82.7%) of maternal participants were recruited to BiB during the glucose tolerance test at 26-28 weeks, some women were recruited retrospectively at other hospital appointments, or whilst postnatal inpatients (McEachan et al., 2024; Wright et al., 2013) so there are some extremely preterm babies in the cohort, but the conclusions that can be made about their outcomes are very limited by the sample size. There were also not many children born moderately preterm in the cohort. Therefore, the decision was made to combine these children in to a <34 week gestation category for the analyses, which although not ideal is consistent with clinical practice as 34 weeks is often a cut-off for whether a baby will be admitted to the neonatal unit in Bradford.

Not all of the covariates of interest could be included in the regression modelling, either due to incompleteness (e.g. breastfeeding) or collinearity. It is possible that other covariates which

were not included in the conceptual model and therefore not adjusted for in the analyses could have a substantial influence on the effect estimates. Other variables included in similar studies but not included in the multivariable models include month of birth (age within the academic year group), maternal height, mode of delivery, previous abortion (or not), firstborn (or not), and parity (Alterman et al., 2021; Mackay et al., 2010). Since it was unclear how these factors might be brought into the conceptual framework, they were not included in the statistical modelling.

For the majority of the analyses including the multivariable modelling all the developmental disorders were combined into 'any developmental disorder'. However, these disorders are heterogeneous and so assuming their relationships with covariates would be consistent was problematic. Ideally all the disorders could have been explored in multivariable analyses individually, but the numbers were too small.

These studies rely upon the accuracy of the coding within the participants' medical records. The codes would have been entered into the children's medical records as part of their health care, i.e. not for research purposes; no specific testing for this research study was carried out. Therefore, absence of a clinical code does not guarantee absence of a disorder. Whilst the NICE guidelines state that developmental disorder is more common in children from ethnic minorities, BiB data shows Asian children are *less* likely than White children to have a developmental disorder, largely as a result of lower incidence rates of ASD, ADHD, and social, emotional, and behavioural problems. As discussed, this may be due to structural inequalities resulting in underdiagnosis (N8 Research Partnership, 2024). Furthermore, Bradford Royal infirmary does not have all tertiary paediatric services, for example paediatric intensive care. It is possible that some children have attended another hospital to receive care, which would have led to an underestimation of the disease burden.

The latent class analysis showed that the children in the 'Typical development' group had a 2.6% chance of a speech language and communication disorder, but a very low probability of any other developmental disorders. This means that some of the children in the regression models in chapter 5 labelled as having a developmental disorder may still go on to experience typical development. The LCA may be more meaningful than the binary outcome used in the models in chapter 5. There is also no way from the binary outcomes to make useful statements about the severity or permanence of a difficulty, which would potentially be useful to both clinicians and parents.

7.6. Conclusion

The work in this thesis represents the most comprehensive study of developmental disorders amongst children born moderately preterm, late preterm, and early term to date, in the form of the systematic review. The secondary data analysis is the largest UK study exploring the association between gestational age and *all* developmental disorders as well as the biggest study of developmental outcomes amongst British born Asian children born before full term.

The majority of developmental disorders are more common in children born before full term which persists when controlling for covariates, and this relationship can even be demonstrated in children born early term. This relationship is also seen among Asian children, which is important since birth before full term is more common among ethnic minorities. The relationship between social deprivation and the incidence of developmental disorders was different for White children and Asian children. The incidence rate of specific developmental disorders was also different for White and Asian children. Further research is required to investigate why this might be the case. Latent class analysis revealed four distinct profiles of co-existence of developmental disorders. The majority of children have 'typical development' and are unlikely to have any diagnosed developmental disorders. Two of the classes of developmental disorder were associated with birth before full term, reflecting different underlying pathophysiological processes. One class was not associated with gestational age, but it is unclear if that is due to the unique socio-demographic makeup of the Born in Bradford cohort. Compared to typical development the risk of membership of the "Educational difficulties" class was increased for all groups of children born before full term, in proportion to the degree of prematurity. The systematic review showed that the most prevalent problem among children born 32-38 weeks gestation was low educational attainment. The results from the latent class analysis suggests this is a result of specific learning difficulties such as dyslexia rather than intellectual disability; better collaboration between health and education services is important for these children, in order that their needs can be met. Knowing who is at risk of which developmental disorders is helpful: it could facilitate earlier and more specific intervention, which could in turn lead to better outcomes and it could allow more effective counselling to be given to families when exploring the chance their preterm baby may go on to have a developmental disorder. However, further research is needed into how and when to do this most effectively.

Appendices

Appendix labelling corresponds to the chapters which the material is relevant to.

Appendix 2.1. Systematic review protocol

Birth before full term and neurodevelopmental disorder: a systematic review and meta-analysis

Review Question: What is the risk of neurodevelopmental disorder in children born between 32-38 weeks gestation?

Searches

Databases:
Medline or PubMed,
Embase
CINAHL,
PsycINFO

Additional sources

PROSPERO register
Google Scholar
The reference lists of articles which are included in the review will be searched to find additional articles which meet the inclusion criteria. The searches will be repeated towards the end of the review process.

Types of study to be included

Any studies which include the exposure and outcome of interest but excluding case studies and case series.

Condition or domain being studied

Every year in England and Wales approximately 52,000 babies are born preterm, before 37 weeks gestation (ONS, 2019). Most research thus far has focussed on the small minority of babies born extremely preterm babies, born at the limits of viability, before 28 weeks gestation (Johnson, 2017). These children have been shown to be at risk of neurodevelopmental disorder such as cerebral palsy; learning disability; communication disorders; attention deficit disorders and autism spectrum disorder (Allotey, 2017). However, the majority of preterm babies are born much closer to term i.e., moderately preterm (32 - 33+6 weeks) or late preterm (34 - 36+6 weeks), and there has been much less research into their outcomes (Boyle, 2013). There are also large numbers of children born at 37-38 weeks gestation ("early term"), sometimes as a result of obstetric intervention, who may also have some increased risk of neurodevelopmental disorder (Quigley, 2012). Understanding children's risk of neurodevelopmental disorder is important; it may allow prompt diagnosis, which has been shown to be associated with improved long-term outcomes (Mandell 2005, Wright 2019). Better understanding of children's risk of neurodevelopmental disorder allows more precise counselling of families, planning of services, and may also be factored into obstetric decision making.

Participants/population

Inclusion criteria:

Must include at least one neurodevelopmental disorder (or special educational need) as an outcome by a standardised test, or physician diagnosis
Estimates provided for children born moderate or late preterm, or early term (32 – 38 weeks)
The mean gestational age of the exposed group must be known (Fong, 2014)

Exclusion criteria:

Interventional/experimental studies
Studies where >10% of the study population were born <32 weeks gestation or the mean gestational age of participants is <32 weeks

Studies where the exposed and comparison groups were dichotomised into <37 or >37 weeks, where no further data on the gestational ages of the exposed group are provided"
Studies reporting adult outcomes, over the age of 18 years.
Studies evaluating the predictive abilities of neuroimaging
Reviews, commentaries, guidelines, editorials, case reports/series, conference proceedings, book chapters
Studies where the exposure is 'small for gestational age' or 'intrauterine growth restriction"
Qualitative studies
Animal studies

Intervention(s), exposure(s)
Birth between 32+0-38+6 weeks gestation
Comparator(s)/control
Birth at full term (39+0 - 41+6 weeks)
Birth <32 weeks
Main outcome(s)
Neurodevelopmental disorder, as defined by The National Institute for Health and Care Excellence:
"A group of problems that become apparent during child development and often occur together. They are characterised by impairments of personal, social, academic, or occupational functioning, ranging from very specific limitations to global impairments of social skills or cognition, as measured by parent or teacher reports and surveillance tools. The term 'disorder' applies if the condition is severe, persistent and pervasive" (NICE, 2017)
This includes, but is not limited to, the following conditions: cerebral palsy; learning disability; communication disorders; attention deficit disorders and autism spectrum disorder (NICE, 2017).
Measures of effect
Adjusted and unadjusted odds ratios with 95% confidence intervals will be extracted from the included studies where possible.
Additional outcome(s)
Special educational need (SEN), if possible, SEN related to neurodevelopmental disorder.
Data extraction (selection and coding)
The search records will be exported into an EndNote library and deduplicated. Screening will be done in a two-stage process. 20% of records will be screened by a second researcher. Any disagreements will be resolved by a third researcher.
Identification of potentially relevant studies by initial screening of the titles and abstracts compared to the inclusion criteria. The screening lists made by each researcher will be merged and a shortlist of records for full review will be created.
Screening of the full text of studies identified as potentially relevant in step 1.
When a record is excluded at the full text stage, the researchers will record why. A flow chart of this process will be generated.
The following information will be extracted from studies:
Basic information: author, year of publication, study design, region
Participants – gestational age range/categories, comparison group used, sample size
Comparison – were the participants compared to children born ≥37 weeks, or 39-41 weeks
Outcome measures – age at which outcome is measured. Method used for assessing outcome
Covariates which were considered / adjusted for e.g., ethnicity, SES, gender
Estimates / findings
Risk of bias (quality) assessment
The quality of included studies will be assessed using the Newcastle-Ottawa Scale as per Wells et al. (Wells, 2021). Funnel plots will be used to assess publication bias.

Strategy for data synthesis

The results will be tabulated and displayed visually. A narrative synthesis of the results will be provided. We will analyse the neurodevelopmental disorder by gestational age at birth: moderately preterm 32-33 weeks and late preterm 34-36 weeks, early term 37-38 weeks, and by age of assessment 2-4 years, 5-11 years, 11-18 years. Potential publication bias will be assessed.

Meta-analysis will be performed where possible, and the I^2 statistic will be used, with values more than 50% indicating substantial heterogeneity. If a meta-analysis is not possible one of the following options will be used, as per the Cochrane handbook (Higgins, 2019):

If effect estimates are provided by the study, but not estimates of variance, then the effect estimates will be summarised using median and interquartile range, which will be tabulated, and displayed graphically as box and whisker plots.

If the statistical tests differ between studies, or only minimal information beyond p-values are provided, but little/no information beyond that, P values may be combined, which will then be presented alongside effect estimates. An albatross plot may be used to display the results.

Analysis of subgroups or subsets

Depending on the outcomes reported by the different studies which are included, we may perform sub-group meta-analyses for specific neurodevelopmental disorders e.g., autism spectrum disorder.

Contact details for further information

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Organisational affiliation of the review

University of York

Review team members and their organisational affiliations

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Clare Copper, University of Leeds
Sarah Blower, University of York
Catherine Hewitt, University of York
Lorna Fraser, University of York
Elaine Boyle, University of Leicester

Type and method of review

Epidemiologic
Prognostic
Systematic review

Anticipated or actual start date

07 December 2021

Anticipated completion date

01 August 2022

Funding sources/sponsors

This review forms part of K. Pettinger's doctoral fellowship, which is funded by the NIHR.

Conflicts of interest

None known

Language

English

Country

England

Appendix 2.2. Systematic review search terms

The following sources were used when designing the search strategy (American University of Beirut, 2024; NICE, 2018 ; Scantlebury, Mcdaid, Dawson et al., 2018; Mpundu-Kaambwa, Chen, Huynh et al., 2017; National Guideline Alliance, 2016; Canadian Health Libraries Association; Canadian Health Libraries Association; Canadian Health Libraries Association; Wolters Kluwer Health).

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to February 08, 2022	**CINAHL complete Ebsco**	**Embase 1996 to 2022 Week 05**	**APA PsycInfo 1806 to January Week 5 2022**
Prematurity and early term concepts			
Infant, Premature, Diseases/ or Infant, Premature/ or premature birth/ OR ("preterm birth" or "gestational age" or (pre-term* adj3 birth*) or (preterm* adj3 birth*) or (pre-term* adj3 born*) or (preterm* adj3 born*)).tw OR ((prematur* adj3 born*) or (prematur* adj3 birth*) or (pre-matur* adj3 born*) or (pre-matur* adj3 birth*)).tw OR (prematurity or pre-maturity or (prematur* adj3 bab*) or (prematur* adj3 infan*) or (pre-matur* adj3 infan*) or (pre-matur* adj3 bab*)).tw OR	(MH "Infant, Premature") OR (TI "preterm birth") OR (AB "preterm birth") OR (TI "pre-term birth") OR (AB "pre-term birth") OR (TI "premature birth") OR (AB "premature birth") OR (TI "gestational age") OR (AB "gestational age") OR (TI pre-term* N3 birth*) OR (AB pre-term* N3 birth*) OR (TI preterm* N3 birth*) OR (AB preterm* N3 birth*) OR (TI pre-term* N3 born*) OR (AB pre-term* N3 born*) OR (TI prematur* N3 born*) OR (AB prematur* N3 born*) OR (TI prematur* N3 birth*) OR (AB prematur* N3 birth*) OR (TI pre-matur* N3 born*) OR (AB pre-matur* N3 born*) OR	exp prematurity/ or ("preterm birth" or "gestational age" or (pre-term* adj3 birth*) or (preterm* adj3 birth*) or (pre-term* adj3 born*) or (preterm* adj3 born*)).tw. or ((prematur* adj3 born*) or (prematur* adj3 birth*) or (pre-matur* adj3 born*) or (pre-matur* adj3 birth*)).tw. or (prematurity or pre-maturity or (prematur* adj3 bab*) or (prematur* adj3 infan*) or (pre-matur* adj3 infan*) or (pre-matur* adj3 bab*)).tw. or ((preterm* adj3 bab*) or (preterm* adj3	premature birth/ or ("preterm birth" or "gestational age" or (pre-term* adj3 birth*) or (preterm* adj3 birth*) or (pre-term* adj3 born*) or (preterm* adj3 born*)).tw. or ((prematur* adj3 born*) or (prematur* adj3 birth*) or (pre-matur* adj3 born*) or (pre-matur* adj3 birth*)).tw. or (prematurity or pre-maturity or (prematur* adj3 bab*) or (prematur* adj3 infan*) or (pre-matur* adj3 infan*) or (pre-matur* adj3 bab*)).tw. or ((preterm* adj3 bab*) or (preterm* adj3

((preterm* adj3 bab*) or (preterm* adj3 infan*) or (pre-term* adj3 bab*) or (pre-term* adj3 infan*)).tw OR	(TI pre-matur* N3 birth*) OR (AB pre-matur* N3 birth*) OR (TI prematurity) OR (AB prematurity) OR (TI pre-maturity) OR (AB pre-maturity) OR (TI prematur* N3 bab*) OR (AB prematur* N3 bab*) OR (TI prematur* N3 infan*) OR (AB	infan*) or (pre-term* adj3 bab*) or (pre-term* adj3 infan*)).tw. or	infan*) or (pre-term* adj3 bab*) or (pre-term* adj3 infan*)).tw. or
((moderate* adj5 preterm*) or (moderate* adj5 pre-term*) or (moderate* adj5 prematur*) or (moderate* adj5 pre-matur*) or (moderate* adj5 birth*) or (moderate* adj5 born*)).tw OR	prematur* N3 infan*) OR (TI pre-matur* N3 bab*) OR (AB pre-matur* N3 bab*) OR (TI pre-matur* N3 infan*) OR (AB pre-matur* N3 infan*) OR (TI preterm* N3 bab*) OR (AB preterm* N3 bab*) OR (TI preterm* N3 infan*) OR (AB preterm* N3 infan*) OR	((moderate* adj5 preterm*) or (moderate* adj5 pre-term*) or (moderate* adj5 prematur*) or (moderate* adj5 pre-matur*) or (moderate* adj5 birth*) or (moderate* adj5 born*)).tw. or	((moderate* adj5 preterm*) or (moderate* adj5 pre-term*) or (moderate* adj5 prematur*) or (moderate* adj5 pre-matur*) or (moderate* adj5 birth*) or (moderate* adj5 born*)).tw. or
((late adj5 preterm*) or (late adj5 pre-term*) or (late adj5 prematur*) or (late adj5 pre-matur*) or (late adj5 birth*) or (late adj5 born*)).tw OR	(TI pre-term* N3 bab*) OR (AB pre-term* N3 bab*) OR (TI pre-term* N3 infan*) OR (AB pre-term* N3 infan*) OR (TI moderate* N5 preterm*) OR (AB moderate* N5 preterm*) OR (TI moderate* N5 pre-term*) OR (AB moderate* N5 pre-term*) OR	((late adj5 preterm*) or (late adj5 pre-term*) or (late adj5 prematur*) or (late adj5 pre-matur*) or (late adj5 birth*) or (late adj5 born*)).tw. or	((late adj5 preterm*) or (late adj5 pre-term*) or (late adj5 prematur*) or (late adj5 pre-matur*) or (late adj5 birth*) or (late adj5 born*)).tw. or
("early term" or "near term" or (early term adj5 birth*) or (early term adj5 born*) or (early term adj5 infan*) or (early term adj5 bab*) or (near term adj5 birth*) or (near term adj5 born*) or (near term adj5 infan*) or (near term adj5 bab*)).tw.	(TI moderate* N5 prematur*) OR (AB moderate* N5 prematur*) OR (TI moderate* N5 pre-matur*) OR (AB moderate* N5 pre-matur*) OR (TI moderate* N5 birth*) OR (AB moderate* N5 birth*) OR (TI moderate* N5 born*) OR (AB moderate* N5 born*) OR	("early term" or "near term" or (early term adj5 birth*) or (early term adj5 born*) or (early term adj5 infan*) or (early term adj5 bab*) or (near term adj5 birth*) or (near term adj5 born*) or (near term adj5 infan*) or (near term adj5 bab*)).tw	("early term" or "near term" or (early term adj5 birth*) or (early term adj5 born*) or (early term adj5 infan*) or (early term adj5 bab*) or (near term adj5 birth*) or (near term adj5 born*) or (near term adj5 infan*) or (near term adj5 bab*)).tw

	(TI late* N5 preterm*) OR (AB late* N5 preterm*) OR (TI late* N5 pre-term*) OR (AB late* N5 pre-term*) OR (TI late* N5 prematur*) OR (AB late* N5 prematur*) OR (TI late* N5 pre-matur*) OR (AB late* N5 pre-matur*) OR (TI late* N5 birth*) OR (AB late* N5 birth*) OR (TI late* N5 born*) OR (AB late* N5 born*) OR (TI “early term") OR (AB ("early term") OR (TI “near term”) OR (AB ("near term”) OR (TI early term N5 birth*) OR (AB early term N5 birth*) OR (TI early term N5 born*) OR (AB early term N5 born*) OR (TI early term N5 infan*) OR (AB early term N5 infan*) OR (TI early term N5 infan*) OR (AB early term N5 infan*) OR (TI early term N5 bab*) OR (AB early term N5 bab*) OR (TI near term N5 birth*) OR (AB near term N5 birth*) OR (TI near term N5 born*) OR (AB near term N5 born*) OR (TI near term N5 infan*) OR (AB near term N5 infan*) OR (TI near term N5 bab*) OR (AB near term N5 bab*)		
185,432	(66,043)	208,281	13,857

NDD concepts			
Child Development/ or Developmental Disabilities/ or (child adj development*).tw. or (((development* or neurodevelopment*) adj disab*) or ((development* or neurodevelopment*) adj disorder*) or ((development* or neurodevelopment*) adj impair*)).tw OR Cerebral Palsy/ or (Cerebral pals* or CP or (motor skills adj disorder*) or (movement* adj disorder*)).tw OR Learning Disabilities/ or Cognition Disorders/ or Intelligence/ or Intellectual Disability/ or Educational Status/ or (intellect* adj (deficien* or difficult* or disab* or disorder* or impair* or handicap*)).tw or ("executive function" or (low* adj2 intellect*)).tw or (learning adj (deficien* or difficult* or disab* or disorder* or handicap* or impair*)).tw or (mental* adj (deficien* or disab* or handicap* or impair*)).tw or "special education* need*".tw or "educational development".tw or "school performance".tw. or "school outcome".tw. or (cogniti* or intelligen* or IQ).tw OR	(MH "Developmental Disabilities") OR (MH "Child Development") OR (MH "Child Development Disorders") or (MH "Neurodevelopment") OR (TI child N2 development*) or (AB child N2 development*) OR (TI development* N2 disorder*) or (AB development* N2 disorder*) OR MH "Motor Skills Disorders" OR MH "Cerebral Palsy" OR (TI Cerebral pals*) or (AB Cerebral pals*) OR (TI motor skills N2 disorder*) or (AB motor skills N2 disorder*) OR (TI movement* N2 disorder*) or (AB movement* N2 disorder*) OR (MH "Intellectual Disability") OR (MH "Learning Disorders") OR (TI "special education* need*") OR (AB "special education* need*") (TI cogniti*) OR (AB cogniti*) OR (TI education* development) OR (AB education* development) OR (TI "school performance") OR (AB "school performance") (TI "school outcome") OR (AB "school outcome") (TI intelligen*) OR (AB intelligen*) OR (TI IQ) OR (AB IQ) OR (TI learning deficien*) OR (AB learning deficien*) (TI learning difficult*) OR (AB learning difficult*)	exp child development/ or exp developmental disorder/ or exp developmental delay/ or (child adj development*).tw. or (((development* or neurodevelopment*) adj disab*) or ((development* or neurodevelopment*) adj disorder*) or ((development* or neurodevelopment*) adj impair*)).tw OR exp cerebral palsy/ or (Cerebral pals* or CP or (motor skills adj disorder*) or (movement* adj disorder*)).tw OR exp learning disorder/ or exp academic underachievement/ or exp intellectual impairment/ or exp intelligence/ or exp cognitive defect/ or (intellect* adj (deficien* or difficult* or disab* or disorder* or impair* or handicap*)).tw. or ("executive function" or (low* adj2 intellect*)).tw. or (learning adj (deficien* or difficult* or disab* or disorder* or handicap* or impair*)).tw. or (mental* adj (deficien* or disab* or handicap* or impair*)).tw or "special education* need*".tw or "educational development".tw or "school performance".tw or "school outcome".tw. or (cogniti* or intelligen* or IQ).tw OR	childhood development/ or exp neurodevelopmental disorders/or delayed development/ or exp developmental disabilities/ or (child adj development*).tw. or (((development* or neurodevelopment*) adj disab*) or ((development* or neurodevelopment*) adj disorder*) or ((development* or neurodevelopment*) adj impair*)).tw OR cerebral palsy/ OR (Cerebral pals* or CP or (motor skills adj disorder*) or (movement* adj disorder*)).tw OR exp learning disorders/ or academic underachievement/ or academic failure/ or intelligence/ or cognitive impairment/ or (intellect* adj (deficien* or difficult* or disab* or disorder* or impair* or handicap*)).tw. or ("executive function" or (low* adj2 intellect*)).tw. or (learning adj (deficien* or difficult* or disab* or disorder* or handicap* or impair*)).tw. or (mental* adj (deficien* or disab* or handicap* or impair*)).tw or "special education* need*".tw or "educational development".tw or "school performance".tw or "school outcome".tw. or (cogniti* or intelligen* or IQ).tw OR

exp Language Disorders/ OR ((language adj disorder*) or (speech adj disorder*)).tw OR "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or child behavior disorders/ or (attenti* adj3 disorder*).tw. or ADHD.tw OR autism spectrum disorder/ or autistic disorder/ or social communication disorder/ or (autism or ASD or "autistic disorder" or "autistic spectrum disorder").tw OR (emotion* adj3 (dysfunction* or disorder* or difficult* or disrupt* or disturb* or problem*)).tw OR	(TI learning disab*) OR (AB learning disab*) (TI learning disorder*) OR (AB learning disorder*) (TI learning impair*) OR (AB learning impair*) (TI learning handicap*) OR (AB learning handicap*) (TI intellectual deficien*) OR (AB intellectual deficien*) OR (TI intellectual difficult*) OR (AB intellectual difficult*) OR (TI intellectual disab*) OR (AB intellectual disab*) OR (TI intellectual disorder*) OR (AB intellectual disorder*) OR (TI intellectual impair*) OR (AB intellectual impair*) OR (TI intellectual handicap*) OR (AB intellectual handicap*) (TI "executive function") OR (AB "executive function") OR (MH "Communicative Disorders”) OR (MH "Language Disorders+") OR (MH "Speech Disorders+") OR (TI speech N2 disorder) OR (AB speech N2 disorder) OR (TI language N2 disorder*) OR (AB language N2 disorder*) OR (MH "Attention Deficit Hyperactivity Disorder") OR (TI attenti* N3 disorder*) or (AB attenti* N3 disorder*) OR (TI ADHD) or (AB ADHD) OR	exp language disability/ OR ((language adj disorder*) or (speech adj disorder*)).tw OR behavior disorder/ or attention deficit disorder/ or (attenti* adj3 disorder*).tw or ADHD.tw OR autism/ or communication disorder/ or (autism or ASD or "autistic disorder" or "autistic spectrum disorder").tw OR (emotion* adj3 (dysfunction* or disorder* or difficult* or disrupt* or disturb* or problem*)).tw OR	speech language pathology/ or exp Language Development/ or exp Language Disorders/ OR ((language adj disorder*) or (speech adj disorder*)).tw OR exp behavior disorders/ or exp attention deficit disorder/ or ((attenti* adj3 disorder*) or ADHD).tw OR exp autism spectrum disorders/ or (autism or ASD or "autistic disorder" or "autistic spectrum disorder").tw OR (emotion* adj3 (dysfunction* or disorder* or difficult* or disrupt* or disturb* or problem*)).tw OR

(feed* adj3 (dysfunction* or disorder* or difficult* or disrupt* or disturb* or delay* or problem*)).tw OR	(MH "Autistic Disorder") OR (TI autism) OR (AB autism) OR (TI ASD) OR (AB ASD) OR (TI “autistic disorder") OR (AB “autistic disorder") OR (TI "autistic spectrum disorder") OR (AB “autistic spectrum disorder”) OR	(feed* adj3 (dysfunction* or disorder* or difficult* or disrupt* or disturb* or delay* or problem*)).tw OR	feeding disorders/ or (feed* adj3 (dysfunction* or disorder* or difficult* or disrupt* or disturb* or delay* or problem*)).tw OR
Sleep Apnea Syndromes/ or sleep apn?ea.tw OR	(TI emotion* n3 dysfunction*) OR (AB emotion* n3 dysfunction*) OR (TI emotion* n3 disorder*) OR (AB emotion* n3 disorder*) OR (TI emotion* n3 difficult*) OR (AB emotion* n3 difficult*) OR	sleep disordered breathing/ or (sleep apn?ea).tw OR exp visual disorder/ or ((low* or handicap* or impair* or partial* or disab* or decrease* or problem* or disorder* or los* or defect*) adj3 (vision or visual* or sight* or eye* or eyesight or sight)).tw OR	sleep apnea/ or (sleep apn?ea).tw OR
vision disorders/ or vision, low/ or ((low* or handicap* or impair* or partial* or disab* or decrease* or problem* or disorder* or los* or defect*) adj3 (vision or visual* or sight* or eye* or eyesight or sight)).tw OR	(TI emotion* n3 disrupt*) OR (AB emotion* n3 disrupt*) OR (TI emotion* n3 disturb*) OR (AB emotion* n3 disturb*) OR (TI emotion* n3 problem*) OR (AB emotion* n3 problem*) OR		exp Vision Disorders/ OR ((low* or handicap* or impair* or partial* or disab* or decrease* or problem* or disorder* or los* or defect*) adj3 (vision or visual* or sight* or eye* or eyesight or sight)).tw OR
	(MH "Feeding and Eating Disorders of Childhood”) OR (TI feed* n3 dysfunction*) OR (AB feed* n3 dysfunction*) OR (TI feed* n3 disorder*) OR (AB feed* n3 disorder*) OR (TI feed* n3 difficult*) OR (AB feed* n3 difficult*) OR (TI feed* n3 disrupt*) OR (AB feed* n3 disrupt*) OR (TI feed* n3 disturb*) OR (AB feed* n3 disturb*) OR (TI feed* n3 problem*) OR (AB feed* n3 problem*) OR		

Hearing Disorders/ or ((low* or handicap* or subnormal* or impair* or partial* or disab* or decrease* or problem* or disorder* or los* or defect*) adj3 hear*).tw	(MH "Sleep Apnea Syndromes+") OR (TI "sleep apn#ea") or (AB "sleep apn#ea") OR (MH "Vision Disorders+") OR (MH "Blindness+") OR (TI partial* N3 vision) OR (AB partial* N3 vision) OR (TI partial* N3 visual) OR (AB partial* N3 visual) OR (TI partial* N3 sight*) OR (AB partial* N3 sight*) OR (TI partial* N3 eyesight*) OR (AB partial* N3 eyesight*) OR (TI problem* N3 vision) OR (AB problem* N3 vision) OR (TI problem* N3 visual) OR (AB problem* N3 visual) OR (TI problem* N3 sight) OR (AB problem* N3 sight) OR (TI problem* N3 eyesight*) OR (AB problem* N3 eyesight*) OR (TI disorder* N3 vision) OR (AB disorder* N3 vision) OR (TI disorder* N3 visual) OR (AB disorder* N3 visual) OR (TI disorder* N3 sight*) OR (AB disorder* N3 sight*) OR (TI disorder* N3 eyesight*) OR (AB disorder* N3 eyesight*) OR (TI los* N3 vision) OR (AB los* N3 vision) OR (TI los* N3 visual) OR (AB los* N3 visual) OR (TI los* N3 sight*) OR (AB los* N3 sight*) OR	Hearing Disorders/ or ((low* or handicap* or subnormal* or impair* or partial* or disab* or decrease* or problem* or disorder* or los* or defect*) adj3 hear*).tw	exp hearing disorders/ or ((low* or handicap* or subnormal* or impair* or partial* or disab* or decrease* or problem* or disorder* or los* or defect*) adj3 hear*).tw

	(TI los* N3 eyesight*) OR (AB los* N3 eyesight*) OR (TI defect* N3 vision) OR (AB defect* N3 vision) OR (TI defect* N3 visual) OR (AB defect* N3 visual) OR (TI defect* N3 sight*) OR (AB defect* N3 sight*) OR (TI defect* N3 eyesight*) OR (AB defect* N3 eyesight*) OR (MH "Hearing Disorders+") OR (TI partial* N3 hearing) OR (AB partial* N3 hearing) OR (TI problem* N3 hearing) OR (AB problem* N3 hearing) OR (TI disorder* N3 hearing) OR (AB disorder* N3 hearing) OR (TI los* N3 hearing) OR (AB los* N3 hearing) OR (TI defect* N3 hearing) OR (AB defect* N3 hearing)		
1,249,508	(429,562)	1,894,461	1,039,674
Total preterm + NDD: 19,059	(6,930)	26,356	4,928
Mortality / labour / anomaly filters			
(preterm* labo?r or pre-term* labo?r or (prematur* adj2 labo?r) or (pre-matur* adj2 labo?r) or ((preterm* adj2 deliver*) or (pre-term* adj2 deliver*) or (prematur* adj2 deliver*) or (pre-matur* adj2 deliver*)) or (wom#n or matern*) or (resus* or (infan* adj3 dea*) or (infan* adj3 mort*) or ((neonat* adj3 dea*) or (neonat* adj3	(TI “preterm labo#r”) OR (AB “preterm labo#r”) OR (TI “pre-term* labo#r”) OR (AB “pre-term* labo#r”) OR (TI prematur* N2 labo#r) OR (AB prematur* N2 labo#r) OR (TI pre-matur* N2 labo#r) OR (AB pre-matur* N2 labo#r) OR	(preterm* labo?r or pre-term* labo?r or (prematur* adj2 labo?r) or (pre-matur* adj2 labo?r) or ((preterm* adj2 deliver*) or (pre-term* adj2 deliver*) or (prematur* adj2 deliver*) or (pre-matur* adj2 deliver*)) or (wom#n or matern*) or (resus* or (infan* adj3 dea*) or (infan* adj3 mort*) or ((neonat* adj3 dea*) or (neonat* adj3	(preterm* labo?r or pre-term* labo?r or (prematur* adj2 labo?r) or (pre-matur* adj2 labo?r) or ((preterm* adj2 deliver*) or (pre-term* adj2 deliver*) or (prematur* adj2 deliver*) or (pre-matur* adj2 deliver*)) or (wom#n or matern*) or (resus* or (infan* adj3 dea*) or (infan* adj3 mort*) or ((neonat* adj3 dea*) or (neonat* adj3

mort*))) or (syndrom* or congenital* or deform*) or (heart* or cardio* or lung* or hypox* or pulmon*)).tw	(TI prematur* N2 deliver*) OR (AB prematur* N2 deliver*) OR (TI pre-matur* N2 deliver*) OR (AB pre-matur* N2 deliver*) OR (TI wom?n or matern*) OR (AB wom?n or matern*) OR (TI resus*) OR (AB resus*) OR (TI infan* N3 dea *) OR (infan* N3 dea*) OR (TI infan* adj3 mort*) OR (AB infan* adj3 mort*) OR (TI neonat* N3 dea*) OR (AB (neonat* N3 dea*) OR (TI neonat* adj3 mort*) OR (TI neonat* adj3 mort*) OR (TI syndrom*) OR (AB syndrom*) OR (TI congenital*) OR (AB congenital *) OR (TI deform*) OR (AB deform*) OR (TI heart)* OR (AB heart*) OR (TI cardi*) OR (AB cardi*) OR (TI lung*) OR (AB lung*) OR (TI hypox*) OR (AB hypox*) OR (TI pulmon*) OR (AB pulmon*)	mort*))) or (syndrom* or congenital* or deform*) or (heart* or cardio* or lung* or hypox* or pulmon*)).tw	mort*))) or (syndrom* or congenital* or deform*) or (heart* or cardio* or lung* or hypox* or pulmon*)).tw.
Imaging filters			
(MRI or neuroimaging or ultrasound).tw or neuroimaging/ or magnetic resonance imaging/ or ultrasonography/	(MH "Neuroradiography") OR (MH "Ultrasonography+") OR (MH "Ultrasonography, Doppler, Transcranial") OR (MH "Magnetic Resonance Imaging+") OR (TI MRI) OR (AB MRI) OR (TI neuroimaging) OR (AB neuroimaging) OR (TI ultrasound) OR (AB ultrasound)	exp echography/ or nuclear magnetic resonance imaging/ or exp neuroimaging/ or (MRI or neuroimaging or ultrasound).tw	exp Magnetic Resonance Imaging/ or exp ultrasound/ or neuroimaging/ or (MRI or neuroimaging or ultrasound).tw.
Qualitative filters			

interviews as topic/ or focus groups/ or narration/ or qualitative research/ or (((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj2 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).tw	(MH "Qualitative Studies") OR (TI ethnography) OR (AB ethnography) OR (TI qualitative) OR (AB qualitative) OR (TI grounded theory) OR (AB grounded theory) OR (TI thematic analysis) OR (AB thematic analysis) OR (TI content analysis) OR (AB content analysis) OR (TI field notes) OR (AB field notes) OR (TI participant observation) OR (AB participant observation) OR (TI narratives) OR (AB narratives) OR (TI field studies) OR (AB field studies) OR (TI focus groups) OR (AB focus groups)	qualitative research/ or ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj2 (interview* or discussion* or questionnaire*)).tw or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant").tw	exp qualitative methods/ or ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj2 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).tw
Guideline filters			
exp Guidelines as topic/ or exp Guideline/ or (guideline* or guidance or (practice adj2 (guide*1 or recommend* or standard*)) or (decision* adj2 (making or make*)) or (evidence-based adj2 (practice* or medicine or nursing))).tw	(MH "Practice Guidelines") OR (TI guideline*) OR (AB guideline*) OR (TI guidance*) OR (AB guidance*) OR (TI practice N2 recommend*) OR (AB practice N2 recommend*) OR (TI decision* N2 mak*) OR (AB decision* N2 mak*)	exp practice guideline/ or (guideline* or guidance or (practice adj2 (guide*1 or recommend* or standard*)) or (decision* adj2 (making or make*)) or (evidence-based adj2 (practice* or medicine or nursing))).tw	exp Best Practices/ or exp Treatment Guidelines/ or exp Professional Standards/ or (guideline* or guidance or (practice adj2 (guide*1 or recommend* or standard*)) or (decision* adj2 (making or make*)) or (evidence-based adj2 (practice* or medicine or nursing))).tw.
Review filters			
exp Review Literature as Topic/ or exp Review/ or Meta-Analysis as Topic/ or Meta-Analysis/ or "systematic review"/ or (((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research	(MH "Systematic Review") OR (MH "Meta Analysis") OR (TI systematic* n3 review*) OR (AB (systematic* n3 review*) OR (TI meta-analy*) OR (AB meta-analy*) OR (TI metaanaly*) OR (AB metaanaly*) OR (TI systematic* n3 bibliographic*) OR (AB systematic* n3 bibliographic*) OR	"systematic review"/ or exp meta analysis/ or (((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj2 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw.	exp "literature review"/ or exp meta analysis/ or exp "systematic review"/ or (((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj2 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw

evidence" or metasynthe* or meta-synthe*).tw	(TI systematic* n3 literature) OR (AB systematic* n3 literature) OR (TI comprehensive* n3 literature) OR (AB comprehensive* n3 literature) OR (TI comprehensive* n3 bibliographic*) OR (AB comprehensive* n3 bibliographic*) OR (TI integrative n3 review) OR (AB integrative n3 review) OR (TI information n2 synthesis) OR (AB information n2 synthesis) OR (TI data n2 synthesi)) OR (AB data n2 synthesis) OR (TI data n2 extract*) OR (AB data n2 extract*)		
Animal filters			
exp animals/ not humans.sh.	(MH "Animals+") NOT (MH "human")	(exp animal/ or nonhuman/) not exp human/	exp animals/ not humans.sh.
9)Trial filters			
(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. or Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or "Randomized Controlled Trial (topic)"/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/ or "Controlled Clinical Trial (topic)"/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studies/ or Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab. or	(MH "randomized controlled trials+") OR (MH "double-blind studies") OR (MH "single-blind studies") OR (MH "random assignment") OR (TI randomi?ed) OR (AB randomi?ed)	exp randomization/ or exp "randomized controlled trial (topic)"/ or exp double blind procedure/ or (random* or sham or placebo* or ((singl* or doubl*) adj (blind* or dumm* or mask*)) or ((tripl* or trebl*) adj (blind* or dumm* or mask*)) or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*)).ti,ab or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab, or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab, . or (pragmatic study or pragmatic studies).ti,ab, or ((pragmatic or practical) adj3 trial*).ti,ab or	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt or clinical trials/ or randomized controlled trials/ or (random* or sham or placebo*).ti,ab or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab or allocated.ti,ab or ((open label or open-label) adj3 (study or studies or trial*)).ti,ab or

((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab. or (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab. or allocated.ti,ab or ((open label or open-label) adj3 (study or studies or trial*)).ti,ab. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab. or (pragmatic study or pragmatic studies).ti,ab. or ((pragmatic or practical) adj3 trial*).ti,ab. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab. or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab		((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab, or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab or (pragmatic study or pragmatic studies).ti,ab or ((pragmatic or practical) adj3 trial*).ti,ab or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab
Diagnostics filters			
(sensitivity or specificity or ((pre-test or pretest) adj probability) or post-test probability or predictive value* or likelihood ratio*).tw.	(TI sensitivity) OR (AB sensitivity) OR (TI specificity) OR (AB specificity) OR (TI pre-test N2 probability) OR (AB pre-test N2 probability) OR (TI pretest N2 probability) OR (AB pretest N2 probability) OR (TI post-test N2 probability) OR (AB post-test N2 probability) OR (TI posttest N2 probability) OR (AB posttest N2 probability) OR (TI “Predictive value”) OR (AB “Predictive value”) OR (TI “likelihood ratio”) OR (AB “likelihood ratio”)	(sensitivity or specificity or ((pre-test or pretest) adj probability) or post-test probability or predictive value* or likelihood ratio*).tw	(sensitivity or specificity or ((pre-test or pretest) adj probability) or post-test probability or predictive value* or likelihood ratio*).tw.
Case report filters			

("Case report*" or "case series").tw.	(TI "Case report*") OR (AB "Case report*") OR (TI "Case series") OR (AB "Case series*")	("Case report*" or "case series").tw.	("case report" or "case series").tw.
Economics filters			
Economics/ or "costs and cost analysis"/ or Cost allocation/ or Cost-benefit analysis/ or Cost control/ or Cost savings/ or Cost of illness/ or Cost sharing/ or "deductibles and coinsurance"/ or Medical savings accounts/ or Health care costs/ or Direct service costs/ or Drug costs/ or Employer health costs/ or Hospital costs/ or Health expenditures/ or Capital expenditures/ or Value of life/ or exp economics, hospital/ or exp economics, medical/ or Economics, nursing/ or Economics, pharmaceutical/ or exp "fees and charges"/ or exp budgets/	(MH Economics+) OR (MH Financial Management+) or (MH Financial Support+) OR (MH Financing, Organized+) OR (MH "Business+) OR (MH Health Resource Allocation+) OR (MH Health Resource Utilization+) OR (TI pharmacoeconomic *) OR (AB pharmacoeconomic *) OR (TI pricing *) OR (AB pricing *)	exp health economics/	exp Economics/ or exp Health Care Economics/
1996 limit			
4,501	2,453	7,382	1,714
4,503 on 10th Feb	2,454	7,382	1,714

Appendix 2.3. Data extraction form

Researcher performing data extraction:	
Date of data extraction:	
Record ID:	
Article title:	
Country of origin (i.e., subjects' location)	
Aim/objectives of the study	
Study design	
Inclusion/exclusion criteria	
data source (e.g., platform study)	
Recruitment procedures used	
Birth years of participants	
Gender - whole cohort unless more than 1% difference between different GA groups	
Ethnicity	
Description of exposure (i.e., weeks)	
How was GA measured description of control (i.e., weeks) both range and mean or median of "term" group	
Definition of the outcome used in study	
Measurement tool or method used	
Binary or continuous outcome	
Age at assessment	
Number of participants enrolled [largest number in study]	
Number of participants included in analysis	
Number of withdrawals, exclusions, lost to follow-up	
prevalence / incidence /cumulative incidence	
Summary outcome data (binary) e.g., number of events, total number of participants	
Summary outcome data (binary) e.g., mean difference, standard deviation, total number of participants	

Appendix 2.4. Studies which met the inclusion criteria but were not meta-analysed because an included study used the same data

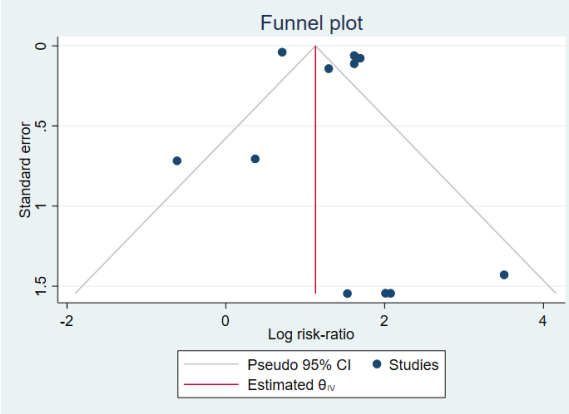
Table 66 - Key characteristics of studies which met the inclusion criteria but were not meta-analysed because an included study used the same data

Ordered by country, then by publication date. SEB: social, emotional, and behavioural disorders; CP: cerebral palsy; DD: developmental delay. Where two or more studies used the same cohort to report the same outcome the most recent paper was used preferentially, unless an older paper reported binary results, which were preferred as they allow the calculation of prevalence.

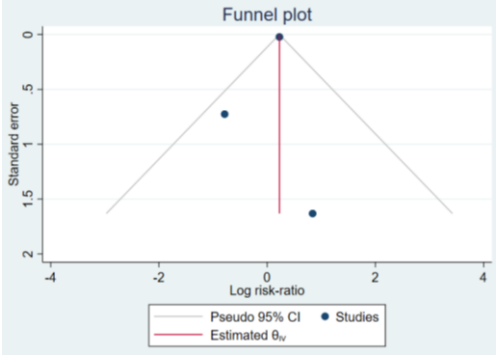
Record ID	Country	Platform study / cohort	Included study using same cohort data	Developmental disorders reported
Nepomnyaschy 2012 (Nepomnyaschy et al., 2012)	USA	Early Childhood Longitudinal Studies Program Birth cohort (ECLS-B)	Woythaler 2011 (binary results presented)	cognitive impairment
Williams 2013 (Berlin et al., 2014)	USA	Georgia Birth to School cohort	Richards 2015	education – aged 6-11 years
Richards 2016 (Richards et al., 2016a)	USA	ECLS-B	Woythaler 2011 (binary results presented)	cognitive impairment
Shah 2016a (Shah et al., 2016a)	USA	ECLS-B	Woythaler 2011 (binary results presented)	developmental delay
Shah 2016b (Shah, Kaciroti, Richards et al., 2016b)	USA	ECLS-B	Woythaler 2015 (binary results presented)	education- school readiness
Beauregard 2018a (Beauregard et al., 2018a)	USA	ECLS-B	Woythaler 2011 (binary results presented)	cognitive impairment
Kerstjens 2011 (Kerstjens et al., 2011)	The Netherlands	Longitudinal Preterm Outcome Project (LoliPOP)	Hornman 2017	developmental delay
Kerstjens 2012 (Kerstjens et al., 2011)	The Netherlands	LoliPOP	Hornman 2017	developmental delay
Potijk 2012 (Potijk et al., 2012)	The Netherlands	LoliPOP	Potijk 2015	SEB
Potijk 2013 (Potijk, Kerstjens, Bos et al., 2013)	The Netherlands	LoliPOP	Hornman 2017	developmental delay
Hornman 2016	The Netherlands	LoliPOP	Potijk 2015	SEB

Record ID	Country	Platform study / cohort	Included study using same cohort data	Developmental disorders reported
(Hornman et al., 2016)				
Potijk 2016 (Potijk et al., 2016)	The Netherlands	LoliPOP	Potijk 2015 (binary results presented)	SEB
Quigley 2012 (Quigley et al., 2012a)	UK	Millennium Cohort Study	Poulsen 2013	education- school readiness
Chan 2014 (Chan and Quigley, 2014)	UK	Millennium Cohort Study	Alterman 2022	education – aged 6 -11 years
Fitzpatrick 2016 (Fitzpatrick et al., 2016)	UK	Millennium Cohort Study	Poulsen 2013 (binary results presented)	cognitive impairment
Beauregard 2018b (Beauregard et al., 2018b)	UK	Millennium Cohort Study	Poulsen 2013 (binary results presented)	education- school readiness
Bentley 2016 (Bentley, 2016)	Australia	AEDC 2009 and 2012 NSW	Hanly 2018	education- school readiness
Arnaud 2007 (Arnaud et al., 2007)	France	Etude Epidemiologique sur les Petits Ages Gestationnels. (EPIPAGE)	Larroque 2008	CP

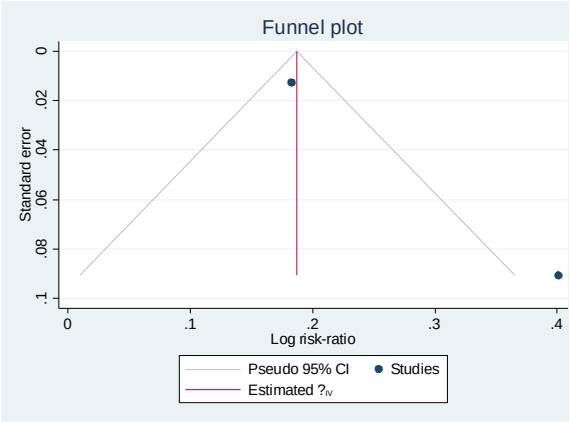
Appendix 2.5. Funnel plots



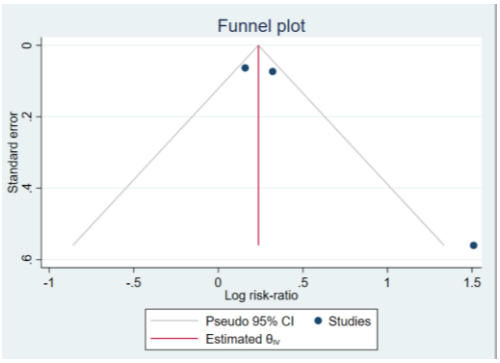
Funnel plot for cerebral palsy meta-analysis, with pseudo 95% confidence limits



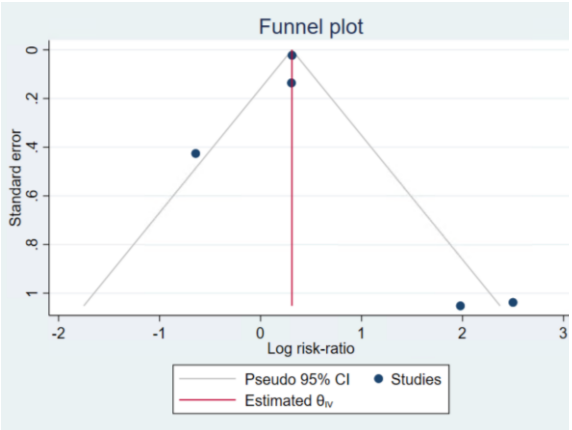
Funnel plot for hearing impairment meta-analysis, with pseudo 95% confidence limits



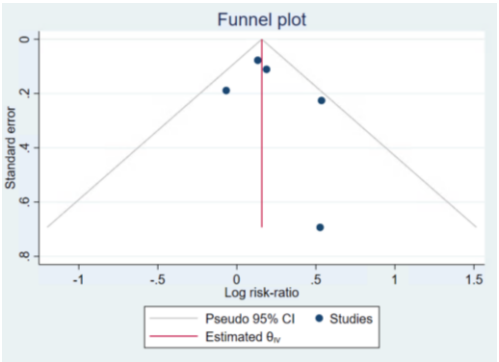
Funnel plot for DCD meta-analysis, with pseudo 95% confidence limits



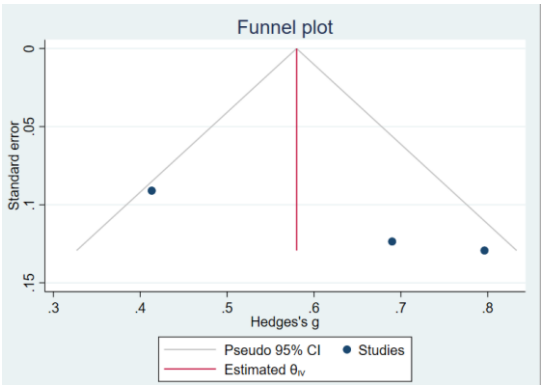
Funnel plot for ASD meta-analysis, with pseudo 95% confidence limits



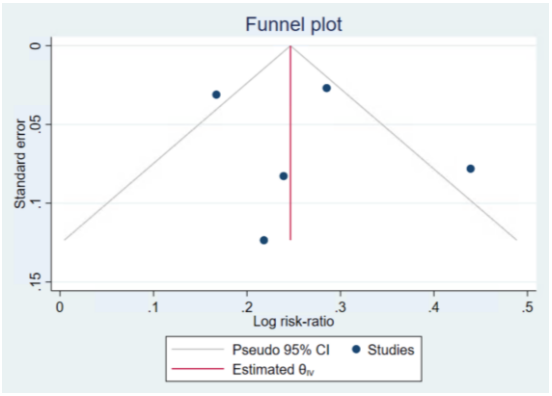
Funnel plot for visual impairment meta-analysis, with pseudo 95% confidence limits



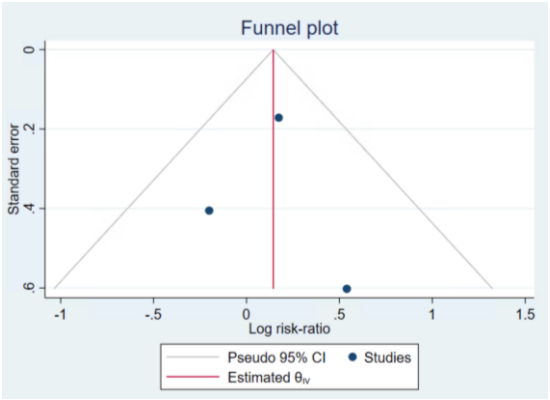
Funnel plot of global social, emotional, and behavioural disorders (binary), with pseudo 95% confidence limits



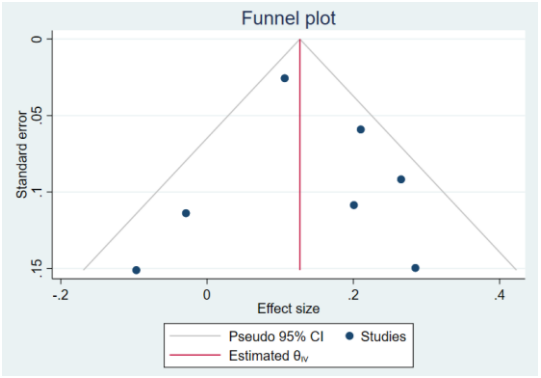
Funnel plot of global social, emotional, and behavioural disorders (continuous), with pseudo 95% confidence limits



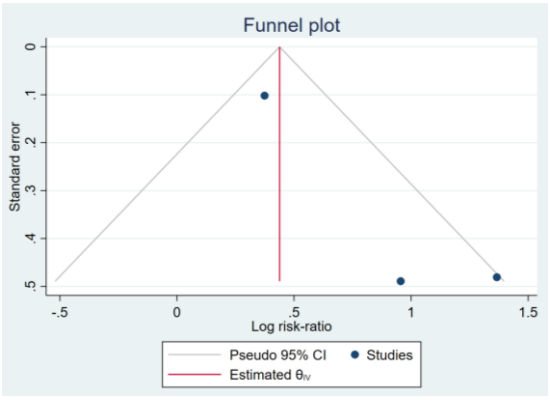
Funnel plot of studies reporting ADHD or ADHD symptoms (binary), with pseudo 95% confidence limits



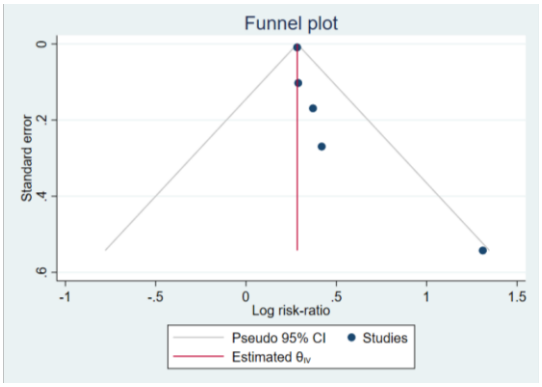
Funnel plot of internalising disorders, with pseudo 95% confidence limits



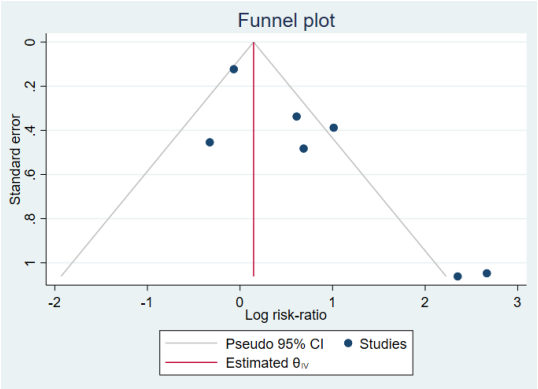
Funnel plot of studies reporting ADHD or ADHD symptoms (continuous), with pseudo 95% confidence limits



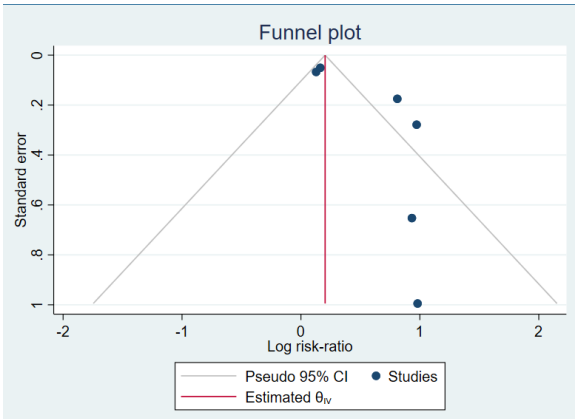
Funnel plot for social problems meta-analysis, with pseudo 95% confidence limits



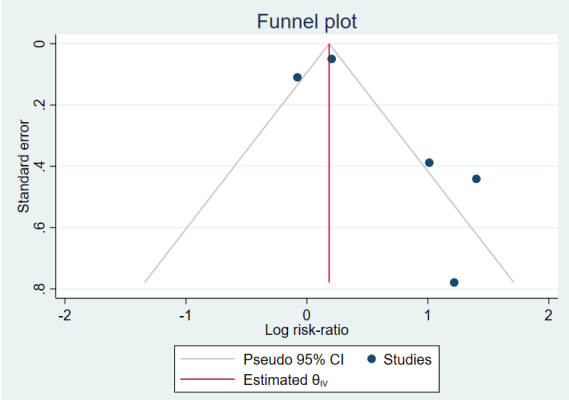
Funnel plot for global developmental delay meta-analysis, with pseudo 95% confidence limits



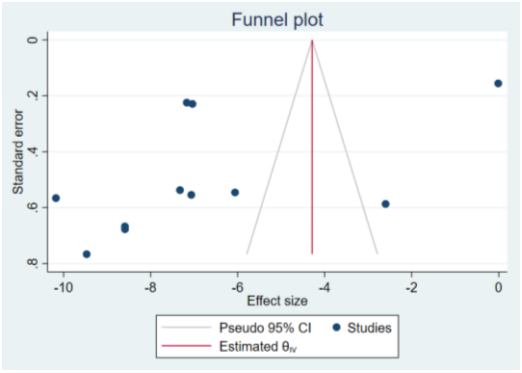
Funnel plot for motor development delay meta-analysis, with pseudo 95% confidence limits



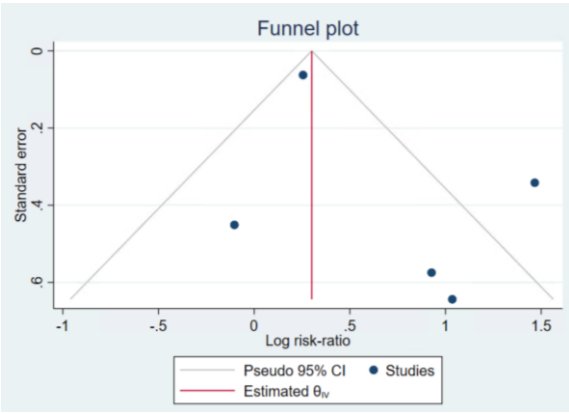
Funnel plot for cognitive impairment (binary measure) meta-analysis, with pseudo 95% confidence limits



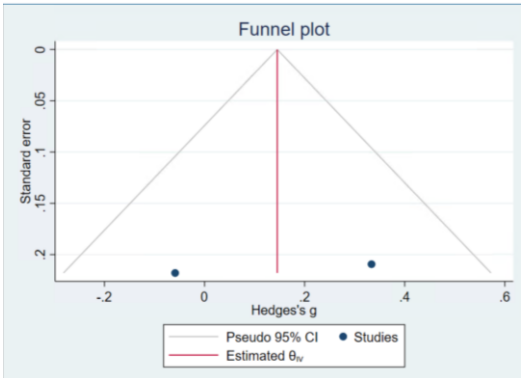
Funnel plot for language developmental delay meta-analysis, with pseudo 95% confidence limits



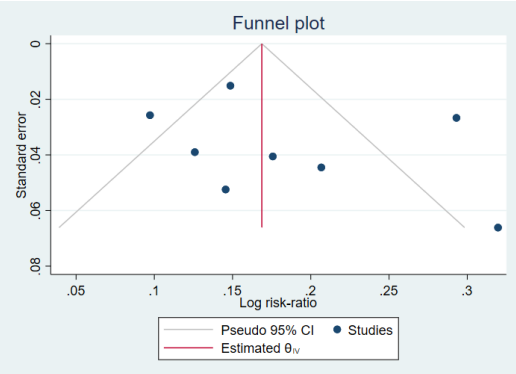
Funnel plot for cognitive impairment (continuous measure) delay meta-analysis, with pseudo 95% confidence limits



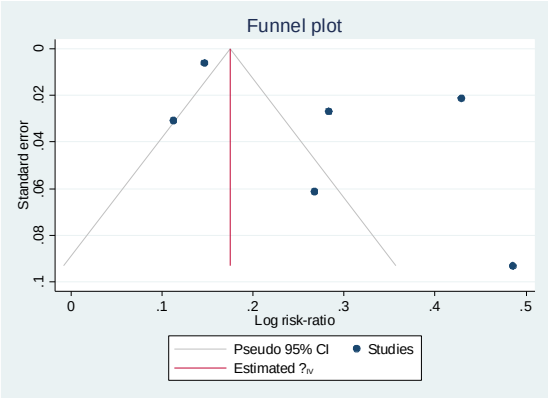
Funnel plot for cognitive developmental delay meta-analysis, with pseudo 95% confidence limits



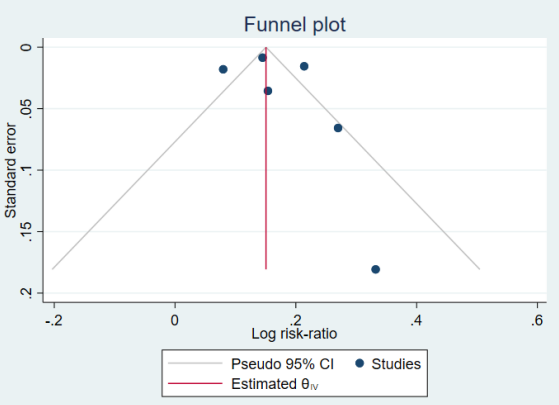
Funnel plot for executive function meta-analysis, with pseudo 95% confidence limits, with pseudo 95% confidence limits



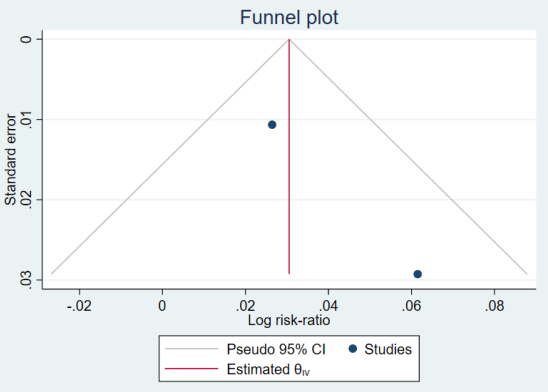
Funnel plot for not school ready meta-analysis, with pseudo 95% confidence limits, with pseudo 95% confidence limits



Funnel plot for special educational needs meta-analysis, with pseudo 95% confidence limits



Funnel plot for poor educational outcomes aged 6- 11 years, with pseudo 95% confidence limits



Funnel plot for poor educational outcomes aged 12-18 years, with pseudo 95% confidence limits

Appendix 2.6. Published version of systematic review

Available at: https://publications.aap.org/pediatrics/article/152/6/e2023061878/195044/Risk-of-Developmental-Disorders-in-Children-Born?autologincheck=redirected

Risk of Developmental Disorders in Children Born at 32 to 38 Weeks' Gestation: A Meta-Analysis

Katherine J. Pettinger, MSc,[a] Clare Copper, MEd,[b] Elaine Boyle, PhD,[c] Sarah Blower, PhD,[a] Catherine Hewitt, PhD,[a] Lorna Fraser, PhD[a,d]

abstract

CONTEXT: Very preterm birth (<32 weeks) is associated with increased risk of developmental disorders. Emerging evidence suggests children born 32 to 38 weeks might also be at risk.

OBJECTIVES: To determine the relative risk and prevalence of being diagnosed with, or screening positive for, developmental disorders in children born moderately preterm, late preterm, and early term compared with term (≥37 weeks) or full term (39–40/41 weeks).

DATA SOURCES: Medline, Embase, Psychinfo, Cumulative Index of Nursing, and Allied Health Literature.

STUDY SELECTION: Reported ≥1 developmental disorder, provided estimates for children born 32 to 38 weeks.

DATA EXTRACTION: A single reviewer extracted data; a 20% sample was second checked. Data were pooled using random-effects meta-analyses.

RESULTS: Seventy six studies were included. Compared with term born children, there was increased risk of most developmental disorders, particularly in the moderately preterm group, but also in late preterm and early term groups: the relative risk of cerebral palsy was, for 32 to 33 weeks: 14.1 (95% confidence intervals [CI]: 12.3–16.0), 34 to 36 weeks: 3.52 (95% CI: 3.16–3.92) and 37 to 38 weeks: 1.44 (95% CI: 1.32–1.58).

LIMITATIONS: Studies assessed children at different ages using varied criteria. The majority were from economically developed countries. All were published in English. Data were variably sparse; subgroup comparisons were sometimes based on single studies.

CONCLUSIONS: Children born moderately preterm are at increased risk of being diagnosed with or screening positive for developmental disorders compared with term born children. This association is also demonstrated in late preterm and early term groups but effect sizes are smaller.

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Dr Pettinger conceptualized and designed the study, performed the literature search, data extraction and data analysis, drafted the initial manuscript, and revised the manuscript; Mrs Copper participated in the literature search and data extraction and critically reviewed the manuscript; Drs Blower, Boyle, Hewitt, and Fraser supervised the study design, the literature search, data extraction and analysis, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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d from http://publications.aap.org/pediatrics/article-pdf/152/6/e2023061878/1578592/peds.2023-061878.pdf

Preterm birth (<37 weeks) is associated with increased risk of developmental disorders, defined as: "heterogeneous conditions that share a disturbance in the acquisition of basic developmental skills in a chronologically appropriate manner."[1]

Most literature focuses on outcomes of children born very (<32 weeks), or extremely preterm (<28 weeks).[2,3] However these represent only 15% of preterm births globally.[4] Emerging evidence suggests early term birth (37–38 weeks) may also affect development.[5,6]

The aim of this review was to determine the relative risk and prevalence of developmental disorders in children born between 32 and 38 weeks' gestation, compared with term born children. Although previous reviews have explored some aspects of this question,[7–10] to our knowledge there are no meta-analyses that have explored outcomes for moderately preterm, late preterm, and early term children and considered all developmental disorders.

Understanding the epidemiology of developmental disorders among children born between 32 and 38 weeks is important, not least because birth at this stage is common: in the United States in 2020, 27.8% of births were early term, 7.4% late preterm (34–36 weeks), and 1.2% moderately preterm (32–33 weeks) (compared with 0.6% extremely preterm).[11] Knowing which disorders are most prevalent among these children could improve targeting of resources and antenatal counseling and potentially avoid delayed diagnosis and missed opportunities for intervention.[12–15]

METHODS

Search Strategy and Selection Criteria

This systematic review was registered with PROSPERO (CRD42021298773) and reported according to PRISMA guidelines.[16] The population of interest was children born between 32 and 38 weeks, aged 2 to 17 years at assessment, born after 1996, when antenatal steroids administration in preterm labor became routine practice.[17] Comparator groups were (where possible) children born at full term (39–40/41 weeks), or if this data were not presented, at term (≥37 weeks) . The outcomes were developmental disorders as per the National Institute for Health and Care Excellence,[18] which in some cases were subdivided further to allow meaningful comparison: cerebral palsy (CP); developmental coordination disorder (DCD); visual impairment; hearing impairment; sleep apnea; oro-motor feeding problems; social, emotional, and behavioral problems subdivided into: global social, emotional, and behavioral problems, internalizing behaviors, externalizing behaviors, and social problems; attention deficit hyperactivity disorder (ADHD); autism spectrum disorder (ASD); developmental delay subdivided into: global developmental delay, language delay, motor developmental delay, and cognitive developmental delay; cognitive impairment; executive function problems; low educational achievement, subdivided into: not "school ready" aged ≤5 years, low educational achievement aged 6 to 11 years, and low educational achievement aged 12 to 17 years; and special educational needs (including physical disabilities which affect learning as well as learning impairments).[19]

Searches were conducted in Medline, Embase, Psychinfo, Cumulative Index of Nursing and Allied Health Literature on February 10, 2022 (updated November 22, 2022). The search terms are listed in Supplemental Table 4. In addition, a Google scholar search was conducted on February 14, 2022. Initially the advanced search feature of Google Scholar was used, but the resulting studies were not relevant. Therefore, a basic search was performed using the question: "What is the risk of neurodevelopmental disorder in children born between 32 and 38 weeks gestation?". The top 50 results were exported. Reference lists of included studies were searched for additional studies that met the inclusion criteria, as follows: at least 1 developmental disorder identified on a validated questionnaire, standardized test, or physician diagnosis; provided estimates for children born moderately or late preterm, or early term.

One author (K.P.) reviewed all titles, abstracts, and full texts using Covidence software.[20] Twenty percent were independently reviewed by a second author (C.C.). There was substantial agreement; 93.6% and Cohen's κ 0.62 at abstract screening; 98.4% and Cohen's κ 0.85 at full text review.[21] Disagreements were resolved by discussion.

Where key data were missing, authors were contacted by e-mail; if no response was received, the study was excluded. Where studies used the same cohort, the most recent publication was included, unless an older study provided the results in a binary format, enabling prevalence calculation (Supplemental Table 5 for summary). The full list of exclusion criteria can be found in the study protocol (CRD42021298773).

Data Extraction

Data were extracted by K.P. and a 20% sample was cross-checked by C.C. for accuracy. See Supplemental Table 3 for data extraction form. Where only odds ratios were presented, the study authors were contacted to request the raw data.

Study Quality

The Newcastle-Ottawa scale was used to assess quality with scores categorized as poor (0–2), fair (3–5), or good (6–9) (Supplemental Fig 11).[22]

Data Analysis

An unadjusted pooled relative risk of each outcome by gestational age was calculated using random effects meta-analysis because of expected heterogeneity, quantified using the I^2 statistic. The number of children with each disorder, the number

without, and the total number of participants (split into gestational subgroups) was used in the calculations. If raw numbers were not presented (or supplied on request), the paper's unadjusted calculated effect sizes (relative risk) were used. When there were 0 cases, a continuity correction of 0.5 was applied. For continuous measures, studies were pooled using Hedge's G standardized mean difference. Signs were changed where necessary.[23] Prevalence was pooled by gestational age with a fixed effect model using the inverse-variance method. The Freeman Tukey double arcsine transformation was specified where necessary to stabilize variances.[24,25] Publication bias was assessed using Egger's test and funnel plots.

Analyses were undertaken by gestational age groupings: moderately preterm (32–33 weeks); late preterm (34–36 weeks); early term (37–38 weeks)[5,26,27]; moderate-to-late preterm (32–36 weeks), but only if results were presented in this format without further breakdown.

Where results were not presented as above, broader groupings were used: 32 weeks was coded as 32–33 weeks; 35–36 weeks was coded as 34–36 weeks; 33–36 weeks, 32–34 weeks, 32–35 weeks, or 32–37 weeks were all coded as 32–36 weeks; and 32–34 weeks and 35–36 weeks were combined into 32–36 weeks.

Where data were available for children born at 32–33 weeks and 34–36 weeks, the 32–36 week category was not presented.

Sensitivity Analysis

Sensitivity analysis was undertaken for relative risk of CP, global developmental delay, and educational outcomes aged 6 to 11 years by comparing results when studies using a ≥37 week term comparison group (as opposed to a 39–40/41 weeks comparison group) were included and excluded.

RESULTS

The initial search identified 11 630 records with 17 further studies from reference screening and updated searches. As shown in Fig 1, 9028 studies were excluded at the first stage and 1462 studies were full text screened; 1386 were excluded, resulting in 76 studies included. There was full agreement between the 2 researchers conducting data extraction.

Study Characteristics

Key characteristics of the included studies are summarized in Table 1. Several studies reported multiple outcomes. All were cohort or cross sectional studies. Sample sizes ranged from 83 to 1 390 601 and covered the full age

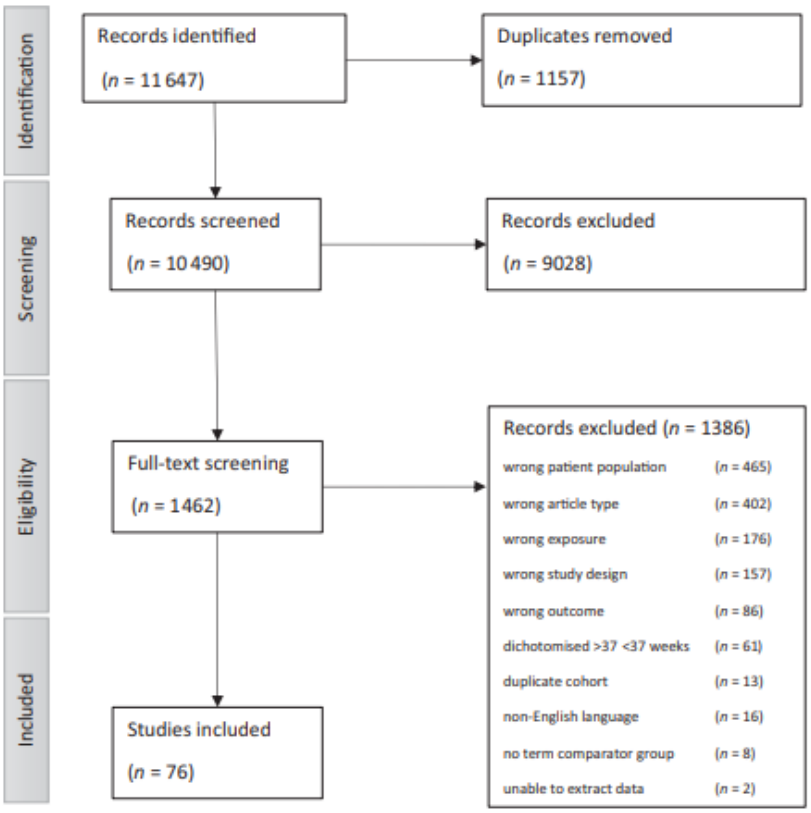

FIGURE 1
Study selection process.

TABLE 1 Key Characteristics of Included Studies Organized by Country, Then by Year of Publication

Record ID	Participants' Country of Origin	Total Participants Included in Meta-analysis	Age at Assessment	Birth Year of Participants	% Male (whole cohort unless ≥1% difference in gestational age groups)	Ethnicity of Participants Using Same Terminology as the Studies (whole cohort or term group)	Developmental Disorders Reported	Study Quality
Baron 2009[53]	United States	34–36 wk: 60; ≥37 wk: 35	3 y	2004–2005	34–36 wk 45%; ≥37 wk 60%	NR	Cognition	Fair
Morse 2009[54]	United States	34–36 wk: 7152; ≥37 wk: 152661 (SEN)	4 y	1996–1997	34–36 wk: 52.2%; ≥37 wk: 51.3%	Black 21.32%; white 55.69%; other 22.98%	SEN, education - not school ready	Good
Petrini 2009[55]	United States	34–36 wk: 8341; 37–41weeks: 128 955 (CP)	1–5 y	2000–2004	34–36 wk: 54.4%; 37–41 wk: 50.9%	Hispanic 24.5%; Asian 18.2%; white 41.5%; unknown 8.5%; Black 7.3%	CP, DD	Good
Baron 2010[56]	United States	35–36 wk: 118; ≥37 wk: 100	3 y	2004–2006	35–36 wk: 50%; ≥37 wk: 60%	Caucasian 72% multiracial 14%; Hispanic: 6%, Asian 4%; African/African American 3%; other 1%	Cognition	Good
Woythaler 2011[57]	United States	34–36 wk: 1200; ≥37 wk: 6300	2 y	2001	34–36 wk: 52.6%; ≥37 wk: 51.4%	White 81.4%; Black 14.3%; other 4.3%	DD	Good
Baron 2012[58]	United States	34–36 wk: 52; ≥37 wk: 195	3 y	2004 and 2006	34–36 wk: 51%; ≥37 wk: 59%	Caucasian 72.7%	Cognition	Fair
Curry 2012[59]	United States	32–33 wk: 3973; 34–36 wk: 21 835; 37–38 wk: 79 228; ≥39 wk 229 626	Up to 3 y	1999–2001	51.3% (NR by gestation)	Hispanic 34.3%, Asian/Pacific Islander 11.9%, Black, non-Hispanic 27.6%, white, non-Hispanic 25.9%, other 0.2%	DD	Good
Talge 2012[60]	United States	3–5 y: 34–36 wk: 96; ≥37 wk 388; 6–9 y: 34–36 wk: 56; ≥37 wk: 222	3–5 y and 6–9 y	1998–2004	48%	White or other 76%; African American 24%	SEB, ADHD	Good
Baron 2014[61]	United States	34–36 wk 410; ≥37 wk: 192	3 y	2004–2008	34–36 wk: 55.4%; ≥37 wk: 53.1%	White 67.7%; other 24%; Hispanic 6.3%; African American: 2.1%	Cognition	Good
Brumbaugh 2014[62]	United States	32–34 wk: 39; 38–42 wk: 44; (cognition)	4 y	2005–2006	32–34 wk:59%; 38–42 wk: 50%	NR	Executive function, cognition	Fair
Kuzniewicz 2014[63]	United States	34–36 wk: 11 945; ≥37 wk 177 129	Minimum 2 y	2000–2007	NR	White: 42%; Hispanic: 24%; Asian: 21%; Black 7%; other 6%	ASD	Good
Richards 2015[64]	United States	34–36 wk: 25 850; 37–41 wk: 29 4076	6–8 y	1998–2002	34–36 wk: 52.9%; 37–41 wk: 50.4%	White non-Hispanic 55.6%; Black non-Hispanic 34.4%; Hispanic 10.0%	Education–aged 6–11 y	Good
Woythaler 2015[65]	United States	34–36 wk 950; ≥37 wk: 4900	5 y	2001	34–36 wk: 53.6%, ≥37 wk 50.4%	White 81.1%; Black: 14.6%; other: 4.3%	Education- not school ready	Good
Hodel 2016[66]	United States	32–36 wk: 45; 37–42 wk: 44; (cognition)	4.5 y	Not stated	32–36 wk: 51.1%; 37–42 wk: 54.3%	Caucasian 92%	Cognition, executive function	Fair
Crockett 2022[67]	United States	34–36 wk: 1339; 39–41 wk: 15 203	Up to age 8	2000–2005	34–36 wk: 53.6%; 39–41 wk: 51.1%	NR	Education- not school ready and aged 6–11 y, ADHD	Good

TABLE 1 Continued

Record ID	Participants' Country of Origin	Total Participants Included in Meta-analysis	Age at Assessment	Birth Year of Participants	% Male (whole cohort unless ≥1% difference in gestational age groups)	Ethnicity of Participants Using Same Terminology as the Studies (whole cohort or term group)	Developmental Disorders Reported	Study Quality
Lingasubramanian 2022[68]	United States	37–38 wk: 400; 39–41 wk: 1022	9 y	1998–2000	52%	Non-Hispanic white 22%; Non-Hispanic Black 48%; Hispanic 27%; another non-white 4%	ADHD	Good
Wehby 2022[69]	United States	32–36 wk 75 017; ≥37 wk: 888 623	6–16 y	2002–2010	51%	White 94%; Black 3%; other3%	Education	Good
Robaei 2006[70]	Australia	32–36 wk: 115; ≥37 wk: 1343 (vision)	6 y	1997–1998	32–36 wk: 52%; ≥37 wk: 51%	White 65.9%; Southeast Asian 15.5%; other 18.5%	Vision	Fair
Raynes-Greenow 2012[71]	Australia	32–36 wk 22 039; ≥37 wk: 377 952	2–6 y	2000–2004	51.4%	NR	Sleep apnea	Good
Schneider 2014[72]	Australia	33–36 wk: 63; 37–41 wk: 44	12 y (mean)	1996–1997	33–36 wk: 57%; 37–41 wk: 52%	NR	Cognition	Good
Smithers 2015[73]	Australia	37–38 wk: 3374; 39–40 wk: 7505	5 y (median)	2004	Whole cohort 50%; (NR by gestation)	Aboriginal and/or Torres Strait Islander 3.3%	Education- not school ready	Good
Cheong 2017[28]	Australia	32–36 wk: 176; ≥37 wk: 150; (SEB - social)	2 y	2009–2012	32–36 wk 47.8%; ≥37 wk 53.2%	NR	DD, SEB, CP	Good
Searle 2017[74]	Australia	32–36 wk: 838; 37–38 wk: 3762; 40 wk: 6224	8 y	2000–2002	50.2% (NR by gestation)	NR	Education–aged 6–11 y	Good
Hanly 2018[46]	Australia	34–36 wk: 3932; 37–38 wk: 20 951; 39–40 wk: 43 199	5 y	2004–2007	Whole cohort 50.7% (NR by gestation)	Aboriginal 7%	Education- not school ready	Good
Brown 2019[75]	Australia	34–36 wk: 76; 37–38 wk: 295; 39–40 wk: 471	8–9 y	2005–2006	52.0% (NR by gestation)	NR	Education– aged 6–11years	Good
Dhamrait 2021[76]	Australia	32–36 wk: 3709; ≥37 wk: 60 675	4–5 y	2004	32–36 wk 52.8%; 37–38 wk 50.8%; 39–40 wk 49.4%	Caucasian 82%; other 12.3%; Indigenous Australian 5.7%	Education- not school ready	Good
Poulsen 2013[77]	UK	32–33 wk: 123; 34–36 wk: 646; 37–38 wk: 2188; 39–41 wk: 8096 (cognition)	3 y	2000–2002	32–33 wk: 59.7%; 39–41 wk: 50.6%	White British: 80% to 89%	Education- not school ready, cognition	Good
Guy 2015[78]	UK	32–33 wk: 82; 34–36 wk: 539; ≥ 37 wk: 749	2 y	2009–2010	NR	98% White in the group with a negative ASD screen	ASD	Fair
Johnson 2015a[3]	UK	32–33 wk: 85; 34–36 wk: 545; 37–42 wk: 750	2 y	2009–2010	32–36 wk: 53.8%; term: 50.2%	White 82.5%, Asian or Asian British 11.2%, Black or Black British 4.4%, Chinese or other 1.0%, Mixed 1.0%	DD	Good
Johnson 2015b[79]	UK	32–33 wk: 84; 34–36 wk: 541; ≥37 wk: 760	2 y	2009–2010	32–36 wk: 53.8%; term: 50.2%	White 78.6%; Asian or Asian British 4.7%; Black or Black British 3.6% Mixed 2.0%; Chinese or other 1.0%; unknown 0.2%	SEB	Good
Cronin 2016[80]	UK	32–33 wk: 164; 34–36 wk: 691; 37–38 wk: 2864; 39–41 wk: 9811	5 y	2002	32–33 wk: 57.3%; 34–36 wk: 53.7%; 37–38 wk: 51.9%; 37–41 wk: 50.6%	White British 87.9%	SEB	Good

TABLE 1 Continued

Record ID	Participants' Country of Origin	Total Participants Included in Meta-analysis	Age at Assessment	Birth Year of Participants	% Male (whole cohort unless ≥1% difference in gestational age groups)	Ethnicity of Participants Using Same Terminology as the Studies (whole cohort or term group)	Developmental Disorders Reported	Study Quality
Pettinger 2020[81]	UK	32–33 wk: 65; 34–36 wk: 478; 37–38 wk: 2355; 39–41 wk: 7269	4 y	2007–2010	52%	English as additional language: 45%	Education - not school ready	Good
Alterman 2021[82]	UK	32–33 wk: 135; 34–36 wk: 732; 37–38 wk: 2460; 39–40 wk 6051	11 y	2000–2002	Whole cohort: 51%; 34–36 wk: 64%	White 87.1%, other 12.9%	SEN	Good
Alterman 2022[83]	UK	32–33 wk: 76; 34–36 wk: 401; 37–38 wk 1408; 39–41 wk: 4896 (education aged 6–11 y)	11 y	2000–2001	32–33 wk: 63.6%; 34–36 wk: 51.4%; 37–38 wk: 52.5%; 39–41 wk: 49.8%	White: 85.2%	Education aged 6–11 y, education aged 12–17 y	Good
Libuy 2022[84]	UK	32–33 wk: 2227; 34–36 wk: 13 385; 37–38 wk: 57 955; 39–40 wk: 156 376	11 y	2004–2005	32–33 wk: 55.1%; 34–36 wk: 54.6%; 37–38 wk: 52.2%; 39–40 wk: 50.5%	White: 78.6%, Asian 10.1%; Black 5.0%, any other ethnic group 1.4%, mixed 4.9%	SEN, education aged 6–11 y	Good
Van Baar 2009[85]	The Netherlands	32–36 wk: 377; ≥37 wk: 182	8 y	1996–1999	32–36 wk: 52%; ≥37 wk: 47%	Dutch 91%	Cognition, SEB	Good
Bul 2012[86]	The Netherlands	32–36 wk: 348; ≥37 wk: 182	8 y	1996–1999	32–36 wk 51.1%, ≥37 wk 47.8%	NR	SEB, ADHD	Good
Cserjesi 2012[87]	The Netherlands	32–36 wk: 248; 38–41 wk: 130	6.9 y (mean)	2002–2003	32–36 wk 55.6%; 38–41 wk 44.6%	NR	Cognition	Good
de Jong 2015[88]	The Netherlands	32–36 wk: 116; 37–41 wk 98; (cognition)	4 y	2010–2011	32–36 wk 57.8%; >37 wk: 45.5%	Dutch 95.9%	Cognition, DD, SEB	Fair
Potijk 2015[89]	The Netherlands	32–36 wk: 915; ≥37 wk: 543	3 y	2002–2003	54.2%	Dutch: 94.6%	SEB	Good
Hornman 2017[90]	The Netherlands	32–36 wk: 644; 38–41 wk: 375	4 y	2002–2003	34–36 wk 58.3%; 38–41 wk 47.1%	Non-Dutch background 4.3%	DD	Good
Hua 2021[91]	China	32–33 wk: 2322; 34–36 wk: 12 915; 37–38 wk: 38 875; 39–40 wk: 76 501	3–5 y	2013–2016	32–33 wk: 54.0%; 34–36 wk: 55.3%; 37–38 wk: 55.3%; 39–40 wk: 51.6%	Han Chinese 99%	Motor	Good
You 2019a[92]	China	34–36 wk: 102; 37–42 wk: 153	24–30 mo	2011–2013	34–36 wk 66.7%; 37–42 wk 61.4%	NR	DD, CP	Good
You 2019b[93]	China	34–36 wk: 112; 37–42 wk: 179	2 y	2013–2015	34–36 wk 54.5%; 37–42 wk 47.5%	NR	DD, CP	Fair
Zhou 2020[45]	China	32–37 wk: 83; 37–42 wk:1665	1 mo–5 y	2011–2016	32–37 wk 51.8%; 37–42 wk 53.8%	NR	DD	Good
Stene-Larsen 2014[94]	Norway	34–36 wk: 1673; 37–38 wk: 7109; 39–41 wk: 30 641	3 y	1999–2008	34–36 wk 51.3%; 37–38 wk: 48.6%; 39–41 wk 50.4%	NR	DD	Good
Strand 2013[95]	Norway	32–36 wk 23 763; 37–40 wk: 522 551	4 y (minimum)	1996–2006	NR - only reported for pre-eclampsia versus no pre-eclampsia	NR	CP	Good
Ask 2018[96]	Norway	34–36 wk: 1755; 37–38 wk: 6732; 40 wk: 11 753 (SEB)	5 y	1999–2008	Whole cohort 51.3% (NR by gestation)	NR	SEB, ADHD	Good
Zambrana 2021[97]	Norway	Total: 26 769	3 y	1999–2008	51.5% (NR by gestation)	NR	DD	Good
Demestre 2016[98]	Spain	34–36 wk: 90; 38–41 wk: 89	4 y	2009	34–36 wk: 61%; 38–41 wk: 55%	NR	DD	Good

TABLE 1 Continued

Record ID	Participants' Country of Origin	Total Participants Included in Meta-analysis	Age at Assessment	Birth Year of Participants	% Male (whole cohort unless ≥1% difference in gestational age groups)	Ethnicity of Participants Using Same Terminology as the Studies (whole cohort or term group)	Developmental Disorders Reported	Study Quality
Oros 2014[99]	Spain	34–36 wk: 6; ≥37 wk: 96	6–13 y	1997–2005	34–36 wk: 40.9%; term 52.6%	Caucasian 99.3%	Cognition	Fair
Pérez-Pereira 2014[100]	Spain	34–36 wk: 47; ≥37 wk: 36	2.5 y	Unclear	34–36 wk: 56.5%; ≥37 wk: 51.4%	NR	Speech	Fair
Pérez-Pereira 2020[101]	Spain	32–33 wk: 31; 34–36 wk: 42; ≥37 wk: 33	5 y	Unclear	52%	NR	Cognition	Good
Klassen 2004[102]	Canada	33–37 wk: 341; >37 wk: 259 (vision)	3.5 y	1996–1997	33–37 wk: 45.2%; >37 wk: 40.2%	NR	DD, hearing, vision	Fair
Leavey 2013[103]	Canada	32–33 wk: 2373; 34–36 wk: 13 108; 37–38 wk: 51 307; 39–41 wk: 146 467	Minimum 3 y	1998–2004	49%	NR	ASD	Good
Faleschini 2020[104]	Canada	32–36 wk: 89; ≥37 wk: 1841	4 y	1997–1998	32–36 wk: 52%; ≥37 wk: 50%	Born in Canada 87%	SEB, ADHD	Good
Chen 2020[105]	Sweden	37–38 wk: 132 997; 39–41 wk: 530 988	3 y	1998–2009	51.1%	NR	Cognition	Good
Beer 2022[106]	Sweden	32–36 wk: 47 859; 37–41 wk: 1 071 729	3–15 y	2002–2014	NR	NR	ADHD	Good
Chen 2022[107]	Sweden	32–36 wk: 77 986; 37–38 wk: 346 859; 39–40 wk: 965 756	0–16 y (median 9.4 y)	1998–2016	50.4% (NR by gestation)	NR	CP	Good
Larsen 2021[108]	Denmark	32–33 wk: 6067; 34–36 wk: 29 821; 37–41 wk: 531 996 (SEN)	4–6 y	1997–2013	NR - it is only reported for each disorder not each gestation	NR	SEN, CP	Good
Zhu 2012[109]	Denmark	32–33 wk: 123; 34–36 wk: 721; 37–38 wk: 3519; 39–40 wk: 11 743	7 y	1996–2002	51%	NR	Motor	Good
Larroque 2008[110]	France	32 wk: 484; 39–40 wk: 389 (vision)	5 y	1997	52% male	NR	Cognition, hearing, vision, CP	Good
Bailhache 2022[111]	France	32–36 wk: 421; ≥37 wk: 4164	9 y	2011	50.9%	NR	SEB, ADHD	Good
Voigt 2012[112]	Germany	32–37 wk: 88; ≥38 wk: 86	2 y	2007–2008	32–37 wk 51%; ≥38 wk 47%	NR	Cognition, SEB, ADHD	Fair
Reuner 2015[113]	Germany	33–36 wk 54; ≥37 wk 38	2 y	2008–2009	33–36 wk: 50%; ≥37 wk: 47%	NR	Cognition	Fair
Darlow 2009[114]	New Zealand	33–36 wk: 112; ≥37 wk: 101	2 y	2001–2002	33–36 wk 61%; term admissions 59%	Māori 5.9%	CP, DD	Good
Berry 2018[115]	New Zealand	33–36 wk: 19 089; 37–38 wk: 70 026; 39–40 wk:180 987 (vision)	6–11 y	1998–2000 and 2005–2015	51.4%	European 67%; Pacific Islander 12%; Māori 21%	SEN, education aged 12–17 y, hearing, vision	Good
Yang 2010[116]	Belarus	38 wk: 2100; 39–41 wk: 11 074	6 y	1996–1997	38 wk: 53.8%; 39 wk: 50.8%; 40 wk: 51.7%	NR	Cognition	Good
Polic 2017[117]	Croatia	34–36 wk: 126; 37–40 wk: 131	6–12 y	2002–2008	34–36 wk: 56.3%; 37–40 wk: 59.5%	NR	SEB	Good

TABLE 1 Continued

Record ID	Participants' Country of Origin	Total Participants Included in Meta-analysis	Age at Assessment	Birth Year of Participants	% Male (whole cohort unless ≥1% difference in gestational age groups)	Ethnicity of Participants Using Same Terminology as the Studies (whole cohort or term group)	Developmental Disorders Reported	Study Quality
Hirvonen 2015[118]	Finland	32–33 wk: 4862; 34–36 wk: 28 152; ≥37 wk: 671 988	7 y	1996–2008	32–33 wk: 54.9%; 34–36 wk: 54.2%; ≥37 wk: 50.8%	NR	CP	Good
Drougia 2007[119]	Greece	34–36 wk 594; ≥37 wk: 1719	Minimum 2 y	1997–2003	NR	NR	CP	Good
Tso 2022[120]	Hong Kong	33–36 wk: 22 811; 37–41 wk: 330 087	6–17 y, mean 11 y 7 mo	2004–2014	52%	NR	ADHD	Good
Patil 2014[121]	India	32–36 wk: 100; ≥37 wk: 100	4–6 y	unclear	Preterm 59%, term 61%	NR	DD	Fair
Marotta 2020[122]	Italy	34–36 wk: 53; ≥37 wk: 53	5–11 y (mean 8)	2002–2010	39.6%	NR	SEB	Fair
Higa Diez 2016[123]	Japan	34–36 wk: 645; 37–38 wk: 5103; 39–41 wk: 11 752	8 y	2001	34–36 wk 60.1%; 37–38 wk 55.3%; 39–41 wk 49.7%	NR	SEB, ADHD	Good
Al-Haddad 2017[124]	Lebanon	32–36 wk: 51; ≥ 37 wk: 69	4.9 y (mean)	2006–2014	55%	NR	Vision	Fair

ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; CP, cerebral palsy; DD, developmental disorder; NA, not applicable; NR, not recorded; SEB, social, emotional, and behavioral disorders; SEN, special educational needs.

range (2–17 years). The majority were from economically developed countries. There were 59 studies rated as "good" quality and 15 as "fair"' (Supplemental Table 7). Two studies were cross sectional, therefore 2 of the Newcastle Ottawa Scale questions did not apply and so were not classified as good, fair, or poor quality. Twenty four meta-analyses were conducted, summarized in Table 2. No papers reported oro-motor feeding problems.

The relative risk of screening positive for, or a diagnosis of, a developmental disorder compared with children born at term, was highest in the moderately preterm group; there was a statistically significant increased relative risk of CP, social problems, ASD, global DD, cognitive impairment, low educational attainment, and special educational needs (Figs 2–9). Forest plots for the remaining disorders are presented in the supplemental information (Supplemental Figs 12–37).

The relative risk of CP compared with children born at term was, for 32 to 33 weeks: 14.1 (95% confidence intervals [CI]: 12.3–16.0), 34 to 36 weeks: 3.52 (95% CI: 3.16–3.92) and 37 to 38 weeks: 1.44 (95% CI: 1.32–1.58). The prevalence of CP per 1000 children was, for 32 to 33 weeks: 17.1 (95% CI: 15.1–19.3), 34 to 36 weeks: 2.95 (95% CI: 2.53–3.39), 37 to 38 weeks: 2.05 (95% CI: 1.91–2.21), and ≥37 weeks: 0.53 (95% CI: 0.50–0.57).

The relative risk of global developmental delay compared with children born at term was, for 32 to 33 weeks: 2.89 (95% CI: 2.77–3.02), 34 to 36 weeks: 1.61 (95% CI: 1.25–2.08) and 37 to 38 weeks: 1.14 (95% CI: 1.12–1.16). The prevalence of global developmental delay per 1000 children was, for 32 to 33 weeks: 350 (95% CI: 335–365), 34 to 36 weeks: 132 (95% CI: 128–136), 37 to 38 weeks: 138 (95% CI: 136–140), and ≥37 weeks: 65.5 (95% CI: 64.7–66.3).

The relative risk of ADHD compared with children born at term was, for 32 to 36 weeks: 1.25 (95% CI: 1.14–1.38), 34 to 36 weeks: 1.62 (95% CI: 1.38–1.90), 37 to 38 weeks: 1.19 (95% CI: 1.00–1.42). The prevalence of ADHD per 1000 children was, for 32 to 36 weeks: 34.9 (95% CI: 33.6–36.3), 34 to 36 weeks: 75.7 (95% CI: 66.1–86.0), 37 to 38 weeks: 37.2 (95% CI: 32.4–42.8), and ≥37 weeks 26.6 (95% CI: 26.3–26.8).

The relative risk of low educational achievement aged 6 to 11 years compared with children born at term was, for 32 to 33 weeks: 1.96 (95% CI: 1.11–3.43), 34 to 36 weeks: 1.21 (95% CI: 1.10–1.32), and 37 to 38 weeks: 1.13 (95% CI: 1.08–1.19). The prevalence of low educational achievement aged 6–11 years per 1000 children was, for 32 to 33 weeks: 304 (95% CI: 285–324), 34 to 36 weeks: 199 (95% CI: 195–203), 37 to 38 weeks: 224 (95% CI: 221–227), and ≥37 weeks: 163 (95% CI: 162–164). A similar pattern is seen across the other developmental disorders, as shown in Supplemental Figs 12–39 (in the supplemental information) and in the prevalence summary bar charts (Fig 10).

Visual or hearing impairment were slightly more prevalent in some of the groups born before full term. The relative risk

TABLE 2 Summary

Developmental Disorder	32–33 wk	32–36 wk	34–36 wk	37–38 wk
CP relative risk	↑	[b]	↑	↑
CP prevalence	↑	[b]	↑	↑
DCD relative risk	↔	[a]	↑	↑
DCD prevalence	↑	[a]	↑	↑
Visual impairment relative risk	↔	↔	[a]	↑
Visual impairment prevalence	↔	↑	[a]	↑
Hearing impairment relative risk	↔	↔	[a]	↑
Hearing impairment prevalence	↓	↑	[a]	↑
Sleep apnea relative risk	[a]	↑	[a]	[a]
Sleep apnea prevalence	[a]	↑	[a]	[a]
SEB global relative risk	↔	[b]	↑	↔
SEB global prevalence	↔	[b]	↑	↔
SEB global (continuous)	[a]	↓	↔	[a]
SEB internalizing relative risk	[a]	↔	↔	[a]
SEB internalizing prevalence	[a]	↔	↑	[a]
SEB externalizing relative risk	[a]	↔	[a]	[a]
SEB externalizing prevalence	[a]	↔	[a]	[a]
SEB social relative risk	↑	[b]	↑	[a]
SEB social prevalence	↔	[b]	↑	[a]
ADHD relative risk	[a]	↑	↑	↑
ADHD prevalence	[a]	↑	↑	↑
ADHD (continuous)	[a]		↑	↔
ASD relative risk	↑	[a]	↑	↔
ASD prevalence		[a]	↑	↓
Global DD relative risk	↑	[b]	↑	↑
Global DD prevalence	↑	[b]	↑	↑
Language DD relative risk	[a]	↔	↔	↔
Language DD prevalence	[a]	↑	↑	↑
Motor DD relative risk	[a]	↔	↔	[a]
Motor DD prevalence	[a]	↑	↔	[a]
Cognitive DD relative risk	[a]	↑	↑	[a]
Cognitive DD prevalence	[a]	↔	↑	[a]
Cognitive impairment relative risk	↑	[a]	↔	↑
Cognitive impairment prevalence	↑	[a]	↑	↑
Cognitive impairment (continuous)	↔	[b]	↑	↑
Executive function (continuous)	[a]	↔	↔	[a]
Not school ready relative risk	↔	[b]	↑	↑
Not school ready prevalence	↑	[b]	↑	↑
Low educational achievement 6–11 y relative risk	↑	[b]	↑	↑
Low educational achievement 6–11 y prevalence	↑	[b]	↑	↑
Low educational achievement 12–17 y relative risk	↔	[b]	↔	↑
Low educational achievement 12–17 y prevalence	↑	[b]	↑	↔
Special educational needs relative risk	↑	[b]	↑	↑
Special educational needs prevalence	↑	[b]	↑	↑

↑, increased RR with CI not crossing "1", or increased prevalence compared with term, with CI not overlapping with term; ↓, reduced RR with CI not crossing "1", or decreased prevalence compared with term, with CI not overlapping with term; ↔, difference not statistically significant. ADHD, attention deficit hyperactivity disorder; DD, developmental disorder; SEB, social, emotional, and behavioral disorders.

[a] No data.

[b] Not presented (data available for both 32–33 wk and 34–36 wk groups).

of visual or hearing impairment compared with children born at term was increased in all gestational subgroups, although this only reached statistical significance in the 37 to 38 week gestation group (Supplemental Figs 15–18). There was a small increased risk and prevalence of sleep apnea but its prevalence is low compared with other disorders (Fig 10).

There is an association with reduced gestational age and increased risk and prevalence of all forms of social,

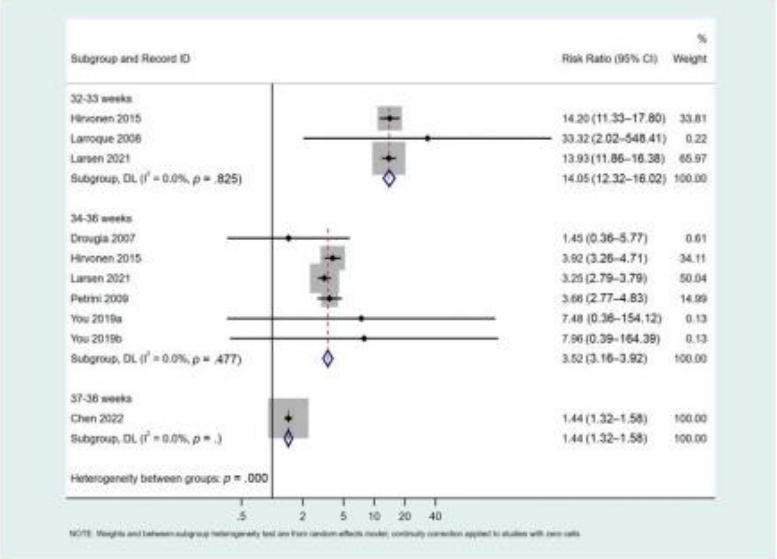

FIGURE 2
Relative risk of cerebral palsy by gestational age.

emotional, and behavioral problems, except externalizing disorders. The most prevalent problem of this type is social problems (eg, showing empathy and playing with other children[28]). There was a small increased risk and prevalence of ASD in the 34 to 36 week group. The only disorder found with neither an increased relative risk nor prevalence among the 32 to 36 week children was externalizing behaviors; this was based on 1 study, as shown in Table 3. There was no increased relative risk of executive function disorders (there is no prevalence estimation since it was reported as a continuous outcome).

Among early term children, prevalence and relative risk of developmental disorder was increased for several disorders: CP, DCD, visual impairment, ADHD, global developmental delay, cognitive impairment, not school ready, low educational achievement, and special education needs (Table 2). There was no data for early term children for: sleep apnea, internalizing behaviors, externalizing behaviors, social problems, motor developmental delay, or cognitive developmental delay.

Sensitivity Analysis

When only the papers with a full term (39–40/41 weeks) comparison group were included, only 1 paper remained in each gestational subgroup for CP and global developmental delay. The overall interpretation was unchanged in all cases (Supplemental Figs 70–73).

Heterogeneity

In general, the heterogeneity statistics (I^2) were 0 (Figs 2–9). Some subgroups had a higher heterogeneity, for example in the educational achievement aged 6 to 11 years meta-analysis (Fig 8). A possible source of heterogeneity was different measurements for developmental disorder; in the CP meta-analysis Larroque 2008, You 2019a, and You 2019b examined participants rather than using linked records, possibly explaining why these studies had a higher prevalence of CP. The different methods used to identify each developmental disorder are shown in Supplemental Table 8. Heterogeneity between subgroups was low.

Publication Bias

The majority of funnel plots (16 of 24) were symmetrical with nonsignificant Egger's tests (14 of 24) (Supplemental Table 9 and Supplemental Figs 48–69 in the supplemental information).

DISCUSSION

Children born between 32 and 38 weeks are at increased risk of screening positive for, or receiving a diagnosis of, a developmental disorder compared with children born at term. In most cases an inverse gradient association with gestational age was demonstrated. The highest increased relative risk compared with children born at term was for children born 32 to 33 weeks for CP, but CP has a low prevalence compared with other developmental disorders.

The association between increased risk and prevalence of global developmental delay or language delay compared with children born at term is evident in all gestational age groups between 32 and 38 weeks. Interpreting

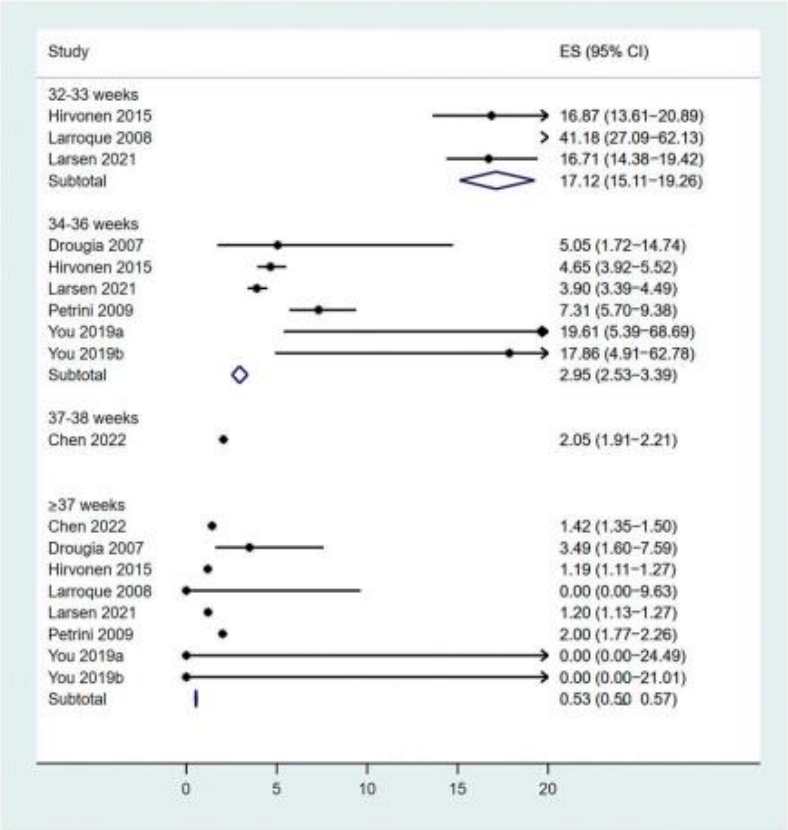

FIGURE 3
Prevalence of cerebral palsy by gestational age.

the cognitive developmental delay meta-analysis is challenging; prevalence was relatively high in the term group, with confidence intervals overlapping the 32 and 36 week group. However, there was an increased relative risk of cognitive developmental delay in the 32 to 36 week group compared with term. It is likely that the picture seen with prevalence is a result of which studies reported different gestational age groups.

In 2 disorders (hearing impairment and ASD), 1 group born 32 to 38 weeks had a lower prevalence of developmental disorder than the term group (Table 2). In both cases this was where the gestational subgroup only included results from 1 study (Table 3). It is likely that this is a peculiarity of the tools used to assess the disorder in that study, since when the relative risks are considered, this effect was not seen.

These findings are largely consistent with previous research that has shown increased risk of developmental disorders among children born moderately preterm, late preterm, and early term.[3,8,10,19] This review demonstrates that difficulties faced by children born 32 to 38 weeks persist through childhood, with evidence of increased risk and prevalence of cognitive impairment and low educational achievement aged 6 to 11 years, in contrast to previous research suggesting developmental delay in preterm infants may be transient.[29,30]

The proportion of children affected by a developmental disorder is generally lower among children born between 32 to 38 weeks compared with extremely preterm children. However, late preterm and early term birth are common; in the United States in 2020, 7.4% of children were born late preterm, whereas only 2.7% were born under 34 weeks.[11] Therefore, small increases in relative risk (compared with full term children) may have a considerable affect, both clinically and economically, at a population level.[30–33]

Developmental disorders affect 35% to 52% of children born extremely or very preterm[31,34] (which is not substantially higher than the prevalence of DCD, social problems, and low educational achievement found in children born 32–38 weeks in this meta-analysis). CP affects 8% to 9% of very preterm children,[29] compared with 1.71% (95% CI: 1.51–1.93) born between 32 and

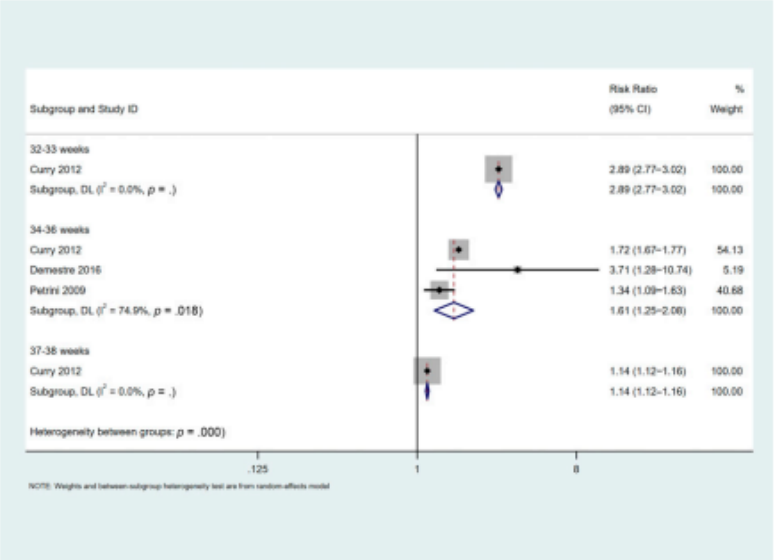

FIGURE 4
Relative risk of global developmental delay by gestational age.

33 weeks in this review. Children born between 32 and 38 weeks may experience a different profile of disorders to extremely preterm children, possibly mediated through different pathways.[13,29,33,35] Birth before full term may be the result of maternal ill health (eg, preeclampsia, gestational diabetes, infection) and a suboptimal intrauterine environment.[33] These antenatal issues may be driving the increased risk and prevalence of developmental disorders, as opposed to the prematurity per se.[7,11,36] Conversely, babies born just a few weeks early have markedly different brain maturation

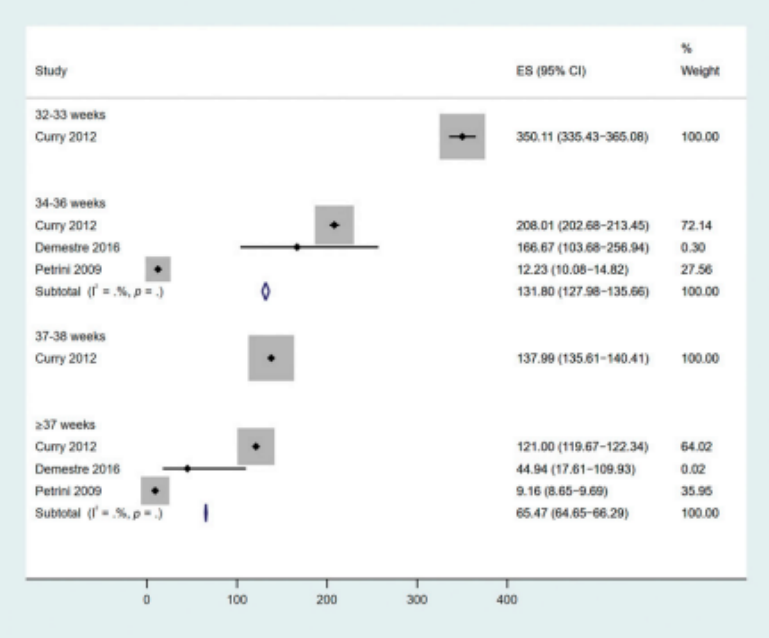

FIGURE 5
Prevalence of global developmental delay by gestational age.

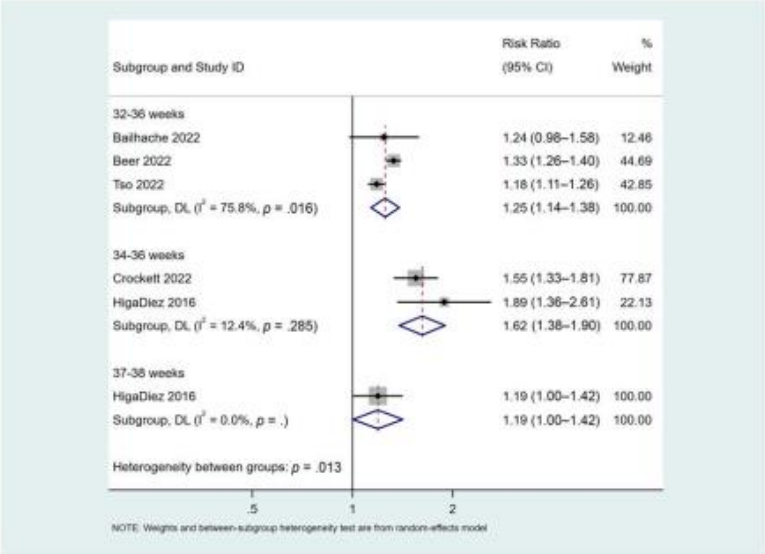

FIGURE 6
Relative risk of ADHD or ADHD symptoms by gestational age.

to full term children.[10,35,37] It is possible that birth between 32 and 38 weeks' gestation may disrupt evolution of neural connections, potentially resulting in developmental disorder.[19,33] Children born before full term are more likely to have medical complications in the immediate neonatal period, in some cases leading directly to a developmental disorder.[19,38] After the neonatal period, children born late preterm are 2 to 3 times more likely to attend the emergency

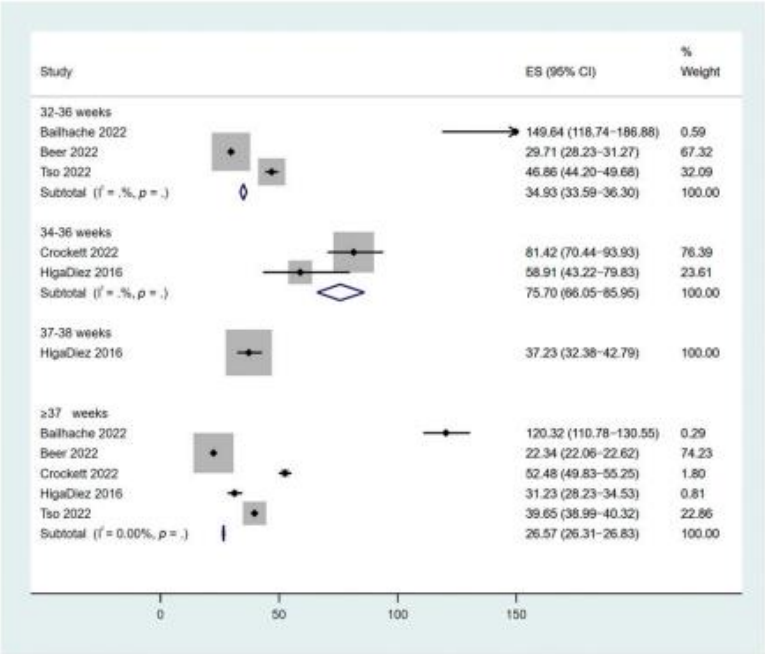

FIGURE 7
Prevalence of ADHD or ADHD symptoms by gestational age.

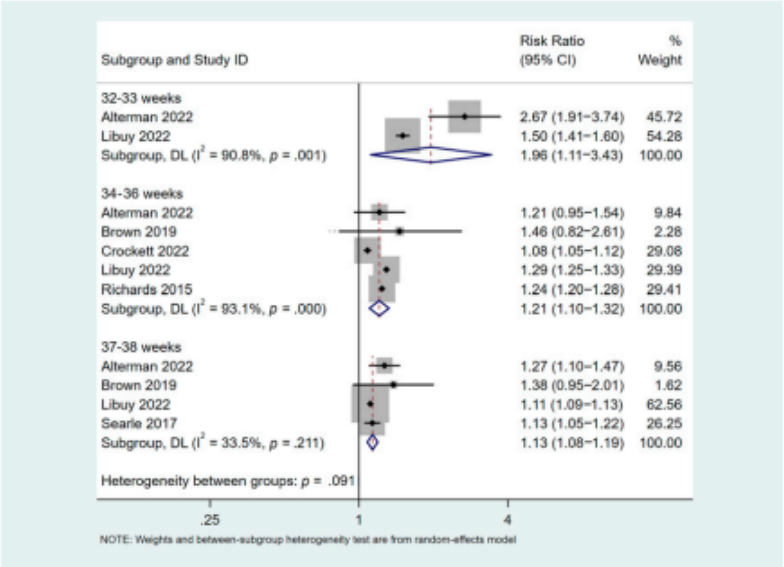

FIGURE 8
Relative risk of low educational achievement aged 6 to 11 years by gestational age.

department or be admitted to hospital.[6,39] The increased medical needs of children born before full term affect both the child and family. Parents of late preterm infants have been shown to have high emotional distress and anxiety levels.[6,40] Furthermore, admission to the neonatal unit is associated with both acute stress and post-traumatic stress disorder among parents.[41] It is plausible that early complications, prolonged admission, or readmission to hospital indirectly affects child development via the negative effect on the whole family.

Strengths and Limitations

This was a broad ranging, comprehensive review. The search strategy identified a large number of studies; there was a total of over 8 million children in the meta-analyses. Including a full range of developmental disorders enabled comparison of prevalence of different developmental disorders across gestational ages. Calculating prevalence meant the increased risk could be contextualized. Although there were a large number of children in total, because each developmental disorder was considered separately according to gestational age subgroups, there were sometimes small numbers in each subgroup (Table 3). There were relatively few studies reporting outcomes for early term children; the subgroup meta-analysis often only contained data from 1 study, although this often represented more children than in the other gestational subgroups combined.

Developmental disorders are, by definition, a heterogeneous group. To determine which conditions to investigate and maximize this review's applicability, we used the NICE guideline, "Developmental follow-up of children and young people born preterm," as a reference.[18] The NICE guideline considers "problems with inattention, impulsivity, or hyperactivity" separately from "executive function problems." However, ADHD is closely associated with impaired executive function, and some have argued that "executive function problems" do not represent a diagnosis as such.[42,43] The NICE guidance also describes increased risk of low educational achievement ("educational attainment" in the UK) among children born preterm. Although there are probably many children who have low educational achievement but do not have a diagnosed developmental disorder, low educational achievement has been demonstrated to be associated with early developmental difficulties.[44] Including educational achievement also gives the opportunity to examine outcomes at a later stage of childhood, demonstrating that the association between birth before full term and developmental disorder can persist into adolescence.

The tools measuring outcomes were numerous and varied, as described in Supplemental Table 8, which likely accounts for some of the different prevalence (eg, DCD Supplemental Fig 13). Furthermore, although some studies used diagnostic codes in medical records to determine their outcome, many studies used questionnaires, tests, and tools (eg, the Ages and Stages Questionnaire) that were not developed to make formal diagnoses, but rather were intended as screening tools for developmental problems.[45] Thus, when considering the results of this review, it is crucial to bear in mind that although some children may screen positive for a potential developmental disorder or be highlighted as a "cause for

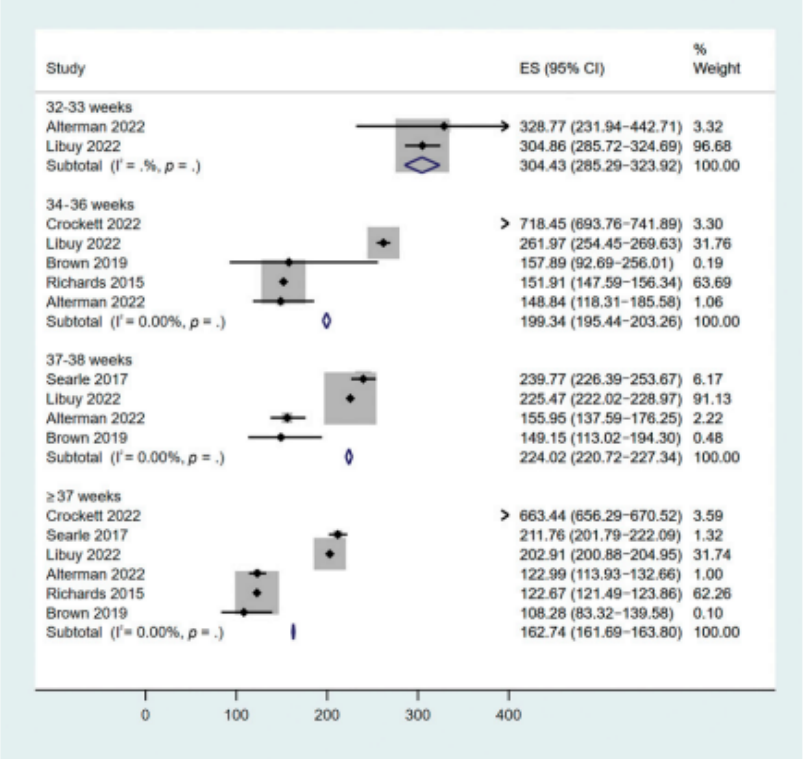

FIGURE 9
Prevalence of low educational achievement aged 6 to 11 years by gestational age.

concern," that does not equate to a formal diagnosis of a specific developmental disorder.

As with other reviews,[10] the children were assessed at different ages and the term comparison groups were variable, for example ≥37 weeks, >37 weeks, ≥39 weeks, 39 to 41 weeks, or 40 weeks. Comparator groups were (where possible) children born at full term (39–40/41 weeks), or if this data were not presented, at term (≥37 weeks). This could account to some extent for why the prevalence of some disorders (eg, not school ready, low educational achievement 6–11 years) is lower in the 37 to 38 week group than in the term group. Although it would have been preferable to have a homogenous term comparator group, only including studies that used a full term (39–40/41 weeks) comparison group would have resulted in a substantial loss of data; of the 76 included studies, only 24 used a full term comparison group. A sensitivity analysis was undertaken for CP, global developmental delay, educational outcomes aged 6 to 11 years, and ADHD, where only the papers with a full term comparison group were included (Supplemental Figs 70–73). In some cases, this resulted in only 1 study in each gestational age subgroup. The overall interpretation was unchanged.

Some studies used atypical cohorts, eg, Drougia 2007, Klassen 2004, and Polic 2017 only included children who admitted to a neonatal unit; in these cases, their term comparator groups would not represent typical term-born children.

The majority of studies were from economically developed countries and all were published in English, possibly limiting generalizability. Outside of the United States, there was limited data on children with non-European heritage; this is important, as race or ethnicity may impact the likelihood of screening positive for, or receiving a diagnosis of, a developmental disorder.[3,18,46]

Implications for Practice

Understanding the long-term implications of birth before full term when balanced against short term risk to the mother and fetus may influence obstetric decision making.[8] It is vital that all healthcare professionals, particularly pediatricians, are well informed of the potential consequences of preterm birth in order that they can give evidence based information to families and so opportunities for early intervention are not missed. Children born at 32 to 38 weeks may benefit from increased monitoring of their development, but most neonatal follow-up programs only apply to children born very preterm, in line with American Academy of Pediatrics guidelines.[6,32,47] However, it is

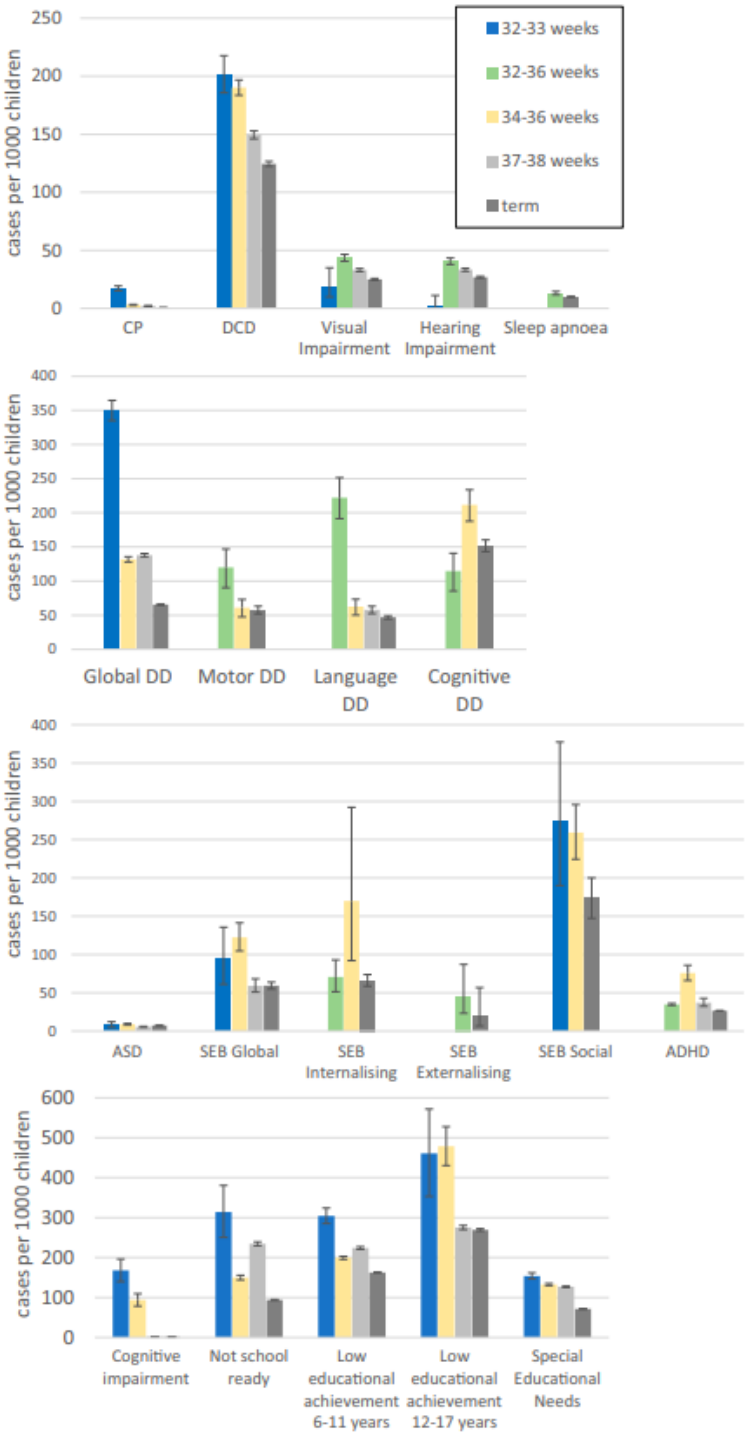

FIGURE 10
Bar chart showing pooled prevalence per 1000 children of developmental disorder by gestational group with 95% confidence intervals.

TABLE 3 Summary Describing the Relative Risk and the Number of Studies and Participants Per Gestational Age Subgroup Per Outcome. Binary Outcomes Unless Specified

Developmental Disorder	32–33 wk	32–36 wk	34–36 wk	37–38 wk	Term	Total
CP						
Relative risk (95% CI)	14.1 (12.3 to 16.0)	NP	3.52 (3.16 to 3.92)	1.44 (1.32 to 1.58)		
Number of children	15 365	NP	87 053	346 859	2 695 512	3 144 789
Number of studies	3	NP	6	1	8	8
DCD						
Relative risk (95% CI)	2.43 (0.82 to 7.25)	ND	1.65 (1.10 to 2.46)	1.15 (1.06 to 1.24)		
Number of children	2445	ND	13 636	42 394	88 244	146 719
Number of studies	2	ND	2	2	2	2
Visual impairment						
Relative risk (95% CI)	7.23 (0.92 to 56.9)	1.42 (0.94 to 2.15)	ND	1.26 (1.20 to 1.32)		
Number of children	484	19 596	ND	70 026	183 047	273 153
Number of studies	1	4	ND	1	5	5
Hearing impairment						
Relative risk (95% CI)	2.32 (0.09 to 56.7)	1.03 (0.35 to 3.04)	ND	1.19 (1.13 to 1.25)		
Number of children	503	19 445	ND	70 053	181 688	271 689
Number of studies	1	2	ND	1	3	3
Sleep apnea						
Relative risk (95% CI)	ND	1.30 (1.15 to 1.46)	ND	ND		
Number of children	ND	22 039	ND	ND	377 952	399 991
Number of studies	ND	1	ND	ND	1	1
SEB global (binary)						
Relative risk (95% CI)	1.12 (0.77 to 1.62)	ND	1.24 (1.04 to 1.48)	1.11 (0.94 to 1.32)		
Number of children	248	ND	1232	2864	10 571	14 915
Number of studies	2	ND	2	1	2	2
SEB global (continuous)						
Standardized mean difference (95% CI)	ND	0.41 (0.23 to 0.59)	0.80 (0.54 to 1.05)	ND		
Number of children	ND	377	126	ND	313	816
Number of studies	ND	1	1	ND	2	2
SEB internalizing						
Relative risk (95% CI)	ND	1.22 (0.89 to 1.69)	0.82 (0.37 to 1.81)	ND		
Number of children	ND	597	53	ND	4368	501
Number of studies	ND	2	1	ND	3	3
SEB externalizing						
Relative risk (95% CI)	ND	2.29 (0.62 to 8.47)	NA	ND		
Number of children	ND	176	NA	ND	151	327
Number of studies	ND	1	NA	ND	1	1
SEB social						
Relative risk (95% CI)	1.51 (1.03 to 2.20)	NP	1.60 (1.04 to 2.46)	ND		
Number of children	84	NP	594	ND	813	1491
Number of studies	1	NP	2	ND	2	2
ADHD (binary)						
Relative risk (95% CI)	ND	1.25 (1.14 to 1.38)	1.62 (1.38 to 1.90)	1.19 (1.00 to 1.42)		
Number of children	ND	7109	2733	5103	1 443 744	1 522 671
Number of studies	ND	3	2	1	5	5
ADHD (continuous)						
Standardized mean difference (95% CI)	ND	0.15 (−0.04 to 0.34)	0.10 (0.06 to 0.15)	0.11 (−0.07 to 0.29)		
Number of children	ND	525	1907	7132	15 494	25 058
Number of studies	ND	3	3	2	7	7
ASD						
Relative risk (95% CI)	1.75 (1.13 to 2.69)	ND	1.42 (1.08 to 1.88)	1.13 (0.98 to 1.29)		
Number of children	2455	ND	25 592	51 307	324 345	403 699
Number of studies	2	ND	3	1	3	3

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TABLE 3 Continued

Developmental Disorder	32–33 wk	32–36 wk	34–36 wk	37–38 wk	Term	Total
Global DD						
Relative risk (95% CI)	2.89 (2.77 to 3.02)	NP	1.61 (1.25 to 2.08)	1.14 (1.12 to 1.16)		
Number of children	3973	NP	30 266	79 228	358 670	472 137
Number of studies	1	NP	3	1	3	3
Language DD						
Relative risk (95% CI)	ND	2.15 (0.98 to 4.70)	1.79 (0.95 to 3.36)	1.53 (0.95, 2.47)		
Number of children	ND	745	1673[a]	7109[a]	31 272[a]	40 799[a]
Number of studies	ND	4	2	2	6	6
Motor DD						
Relative risk (95% CI)	ND	1.69 (0.99 to 2.88)	4.26 (0.53 to 34.4)	ND		
Number of children	ND	522	1414	ND	7108	9044
Number of studies	ND	4	3	ND	7	7
Cognitive DD						
Relative risk (95% CI)	ND	2.32 (1.08 to 4.99)	1.29 (1.14 to 1.46)	ND		
Number of children	ND	525	1200	ND	6780	8505
Number of studies	ND	4	1	ND	5	5
Cognitive impairment (binary)						
Relative risk (95% CI)	1.86 (1.39 to 2.48)	ND	1.86 (0.93 to 3.72)	1.16 (1.07 to 1.27)		
Number of children	631	ND	1315	135 185	540 350	677 481
Number of studies	3	ND	4	2	6	6
Cognitive impairment (continuous)						
Standardized mean difference (95% CI)	−0.07 (−0.56 to 0.41)	NP	−0.31 (−0.54 to −0.08)	−0.60 (−1.15 to −0.05)		
Number of children	31	NP	564	469	11 529	12 593
Number of studies	1	NP	4	1	5	5
Executive function (continuous)						
Standardized mean difference (95% CI)	ND	0.33 (−0.08 to 0.74)	−0.06 (−0.49 to 0.37)	ND		
Number of children	ND	45	39	ND	90	174
Number of studies	ND	1	1	ND	2	2
Not school ready relative risk						
Relative risk (95% CI)	1.28 (0.94 to 1.76)	NP	1.31 (1.23 to 1.39)	1.11 (1.08, 1.14)		
Number of children	199	NP	14 485	29 238	239 737	283 659
Number of studies	2	NP	6	4	7	7
Low educational achievement 6–11 yrs						
Relative risk (95% CI)	1.96 (1.11 to 3.43)	NP	1.21 (1.10 to 1.32)	1.13 (1.08, 1.19)		
Number of children	2215	NP	40 586	60 995	472 354	576 150
Number of studies	2	NP	5	4	6	6
Low educational achievement 12–17 yrs						
Relative risk (95% CI)	1.04 (0.82 to 1.33)	NP	1.08 (0.97 to 1.21)	1.03 (1.01 to 1.05)		
Number of children	76	NP	401	28 948	83 073	112 498
Number of studies	1	NP	1	2	2	2
Special educational needs						
Relative risk (95% CI)	1.60 (1.25 to 2.04)	NP	1.36 (1.23 to 1.51)	1.17 (1.09 to 1.26)		
Number of children	8429	NP	53 178	129 778	1 053 459	1 244 844
Number of studies	3	NP	5	3	6	6

ND, data; NP, not presented (data available for both 32–33 wk and 34–36 wk groups).
[a] This does not include Zambrana 2021, as only the results of the regression were presented, therefore the raw numbers could not be extracted.

likely that, especially among the more mature gestations, many children will not have any developmental disorders.[31] Depending on the structure and financing of the healthcare systems, routine appointments for all these children may be impractical and undesirable. A more effective approach would be collaborating with the education sector (which currently bears the majority of the cost associated with prematurity[48]). Teachers should be informed if they have students who are born preterm and early term and receive training on how to support them.[8,49] It is also likely that early childhood risks for poorer outcomes are additive; determining which groups of children born 32 to

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38 weeks are most at risk for developmental disorder, selectively following them up, and providing family support would be a pragmatic approach.[6] Empowering parents with information on developmental risks is important, not only for the early recognition of problems, but also to give parents agency.[47] It is currently unclear which children born between 32 and 38 weeks are at the highest risk[32] or to what extent early interventions shown to benefit very preterm children might also benefit children born 32 to 38 weeks.[12,32,48–52]

We have demonstrated that for many gestational subgroups the research into developmental disorders is sparse (Table 3) and gaps in the empirical knowledge persist. In future research, consistent outcome measurements, full term control groups (39–40/41 weeks) and standardized gestational age groups should be used, to allow easier comparison.[8,19,32]

CONCLUSIONS

This review has found evidence of an inverse relationship between birth before full term and the majority of developmental disorders. Low educational achievement, DCD, global developmental delay, and cognitive impairment were the most prevalent disorders among children born 32 to 38 weeks. Some of the increased risks are small but may have significant consequences both clinically and economically at a population level, as birth between 32 and 38 weeks is common. Future research should focus on determining which subgroups of children born 32 to 38 weeks are at particularly high risk and how these children can be supported to reach their potential.

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ABBREVIATIONS

ADHD: attention deficit hyperactivity disorder
ASD: autism spectrum disorder
CI: confidence interval
CP: cerebral palsy
DCD: developmental coordination disorder

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Appendix 4.1. Characteristics of analysis cohort by exposure (gestational age)

Table 67 - Proportion of children in the analysis cohort in each gestational category by neonatal characteristics

Characteristics	<34 weeks	34-36 weeks	37-38 weeks	39-41 weeks	>41 weeks	total
NEONATAL CHARACTERISTICS						
Child's Sex						
Boys	120	326	1,545	4,713	97	6,801
Percentage	1.8%	4.8%	22.7%	69.3%	1.4%	
Girls	94	280	1,405	4,509	83	6,371
Percentage	1.5%	4.4%	22.1%	70.8%	1.3%	
Total	214	606	2,950	9,222	180	13,172
Percentage	1.6%	4.6%	22.4%	70.0%	1.4%	
Multiplicity						
Singletons	177	525	2,765	9,220	180	12,867
Percentage	1.4%	4.1%	21.5%	71.7%	1.4%	100%
Twins	37	81	185	*	*	305
Percentage	12.1%	26.6%	60.7%			100%
Total	214	606	2,950	9,222	180	13,172
Percentage	1.6%	4.6%	22.4%	70.0%	1.4%	100%
Admitted to Special Care Baby Unit						
Admitted	125	169	*	210	*	620
Percentage	20.2%	27.3%		33.9%		100%
Not admitted	44	304	2,280	7,283	146	10,057
Percentage	0.4%	3.0%	22.7%	72.4%	1.5%	100%
Total	169	473	2,393	7,493	149	10,677
Percentage	1.6%	4.4%	22.4%	70.2%	1.4%	100%
Small for gestational age (SGA)						
SGA	24	61	274	1,397	39	1,795
Percentage	1.3%	3.4%	15.3%	77.8%	2.2%	100%
Not SGA	152	464	2,491	7,823	137	11,067
Percentage	1.4%	4.2%	22.5%	70.7%	1.2%	100%
Total	176	525	2,765	9,220	176	12,862
Percentage	1.4%	4.1%	21.5%	71.7%	1.4%	100%
Large for gestational age (LGA)						
LGA	*	49	246	602	*	918
Percentage		5.3%	26.8%	65.6%		100%
Not LGA	164	476	2,519	8,618	167	11,944
Percentage	1.4%	4.0%	21.1%	72.2%	1.4%	100%
Total	176	525	2,765	9,220	176	12,862
Percentage	1.4%	4.1%	21.5%	71.7%	1.4%	100%

** data suppressed*

Table 68 - Proportion of children in the analysis cohort in each gestational category by antenatal characteristics

Characteristics	<34 weeks	34-36 weeks	37-38 weeks	39-41 weeks	>41 weeks	total
ANTENATAL CHARACTERISTICS						
Mother's age						
Median (range)	28 (16-44)	27 (15-44)	28 (15-45)	27 (15-49)	26 (16-42)	27 15-49
Mean (SD)	28.2 (6.0)	27.8 (5.7)	28.3 (5.6)	27.3 (5.5)	26.6 (5.7)	27.5 (5.6)
Total	214	606	2,950	9,222	180	13,172
Parity						
Median (range)	0 (0-8)	1 (0-7)	1 (0-10)	1 (0-10)	0 (0-5)	1 (0-10)
Mean (SD)	0.98 (1.43)	1.11 (1.32)	1.33 (1.38)	1.12 (1.27)	0.69 (1.10)	1.16 (1.30)
Total	209	595	2,817	8,891	172	12,684
Pre-eclampsia						
Yes Percentage	*	57 16.7%	117 34.3%	136 40.0%	*	341 100%
No Percentage	167 1.4%	512 4.2%	2,678 22.0%	8,712 71.2%	171 1.4%	12,240 100%
Total	196 1.6%	569 4.5%	2,795 22.2%	8,848 70.3%	173 1.4%	12,581 100%
Gestational diabetes						
Yes Percentage	*	66 6.3%	679 64.7%	286 27.3%	*	1,049 100%
No Percentage	191 1.6%	531 4.4%	2,248 19.0%	8,887 73.8%	178 1.5%	12,035 100%
Total Percentage	208 1.6%	597 4.6%	2,927 22.4%	9,173 70.1%	179 1.4%	13,084 100%
Type of Labour onset						
Spontaneous Percentage	129 1.4%	372 4.1%	1,684 18.5%	6,842 75.2%	73 0.8%	9,100 100%
Caesarean Percentage	73 6.4%	99 8.7%	390 34.2%	572 50.1%	7 0.6%	1,141 100%
Elective C/S Percentage	*	17 6.2%	96 34.9%	157 57.1%	*	275 100%
Any induction Percentage	*	117 4.4%	776 29.4%	1,644 62.2%	*	2,644 100%
Total Percentage	214 1.6%	605 4.6%	2,946 22.4%	9,215 70.0%	180 1.4%	13,160 100%

*C/S = Caesarean section; * data suppressed*

Table 69 - Proportion of children in the analysis cohort in each gestational category by sociodemographic characteristics

Characteristics	<34 weeks	34-36 weeks	37-38 weeks	39-41 weeks	>41 weeks	total
SOCIODEMOGRAPHIC CHARACTERISTICS						
Socio-economic position – five group latent class analysis						
Least deprived most educated	36	96	447	1,485	32	2,096
Percentage	1.7%	4.6%	21.3%	70.9%	1.5%	100%
Emp not mat deprived	51	82	448	1,536	43	2,160
Percentage	2.4%	3.8%	20.7%	71.1%	2.0%	100%
Emp no access to money	15	71	386	1,161	23	1,656
Percentage	0.9%	4.3%	23.3%	70.1%	1.4%	100%
Benefits but coping	54	124	753	2,235	35	3,201
Percentage	1.7%	3.9%	23.5%	69.8%	1.1%	100%
Most deprived	24	105	375	1,201	25	1,730
Percentage	1.4%	6.1%	21.7%	69.4%	1.5%	100%
Total	180	478	2,409	7,618	158	10,843
Percentage	1.7%	4.4%	22.2%	70.3%	1.5%	100%
Index of Multiple Deprivation (IMD) group						
1 (most deprived)	133	323	1,613	5,102	101	7,272
Percentage	1.8%	4.4%	22.2%	70.2%	1.4%	100%
2	18	90	456	1,378	28	1,970
Percentage	0.9%	4.6%	23.2%	70.0%	1.4%	100%
3	22	45	262	850	20	1,199
Percentage	1.8%	3.8%	21.9%	70.9%	1.7%	100%
4	*	11	52	211	*	286
Percentage		3.9%	18.2%	73.8%		100%
5 (least deprived)	*	14	41	116	*	175
Percentage		8.0%	23.4%	66.3%		100%
Total	180	483	2,424	7,657	158	10,902
Percentage	1.7%	4.4%	22.2%	70.2%	1.5%	100%
Means tested benefits						
Yes	65	200	1,083	3,097	51	4,496
Percentage	1.5%	4.5%	24.1%	68.9%	1.1%	100%
No	114	283	1,329	4,540	107	6,373
Percentage	1.8%	4.4%	20.9%	71.2%	1.7%	100%
Total	179	483	2,412	7,637	158	10,869
Percentage	1.7%	4.4%	22.2%	70.3%	1.5%	100%
Mother's highest educational qualification (equivalised if foreign)						
<5 GCSE	39	126	565	1,609	29	2,368
Percentage	21.%	26.6%	23.6%	21.3%	18.5%	22.0%
5 GCSE	49	126	750	2,374	51	3,350
Percentage	27.4%	26.6%	31.3%	31.4%	32.5%	31.1%
A-level	36	64	342	1,123	25	1,590
Percentage	20.1%	13.5%	14.3%	14.9%	15.9%	14.8%
> A-level	41	126	565	1,954	40	2,726
Percentage	22.9%	26.6%	23.6%	25.9%	25.5%	25.3%

Characteristics	<34 weeks	34-36 weeks	37-38 weeks	39-41 weeks	>41 weeks	total
other or unknown	14	31	172	495	12	724
Percentage	7.82%	6.55	7.18	6.55	7.64	6.73
Total	179	473	2,394	7,555	157	10,758
Percentage	100	100	100	100	100	100
Child's Ethnicity						
White	89	240	954	3,630	88	5,001
Percentage	1.8%	4.8%	19.1%	72.6%	1.8%	100%
Mixed	10	35	157	489	13	704
Percentage	1.4%	5.0%	22.3%	69.5%	1.9%	100%
Asian	107	307	1,739	4,745	72	6,970
Percentage	1.5%	4.4%	25.0%	68.1%	1.0%	100%
Black	*	17	51	169	*	245
Percentage		6.9%	20.8%	69.0%		100%
Other	*	*	36	130	*	179
Percentage			20.1%	72.6%		100%
Total	213	606	2,937	9,163	180	13,099
Percentage	1.6%	4.6%	22.4%	70.0%	1.4%	100%
Consanguinity (Mother related to baby's father other than by marriage)						
Yes	44	143	835	2,265	41	3,328
Percentage	1.3%	4.3%	25.1%	68.1%	1.2%	100%
No	136	341	1,587	5,387	117	7,568
Percentage	1.8%	4.5%	21.0%	71.2%	1.6%	100%
Total	180	484	2,422	7,652	158	10,896
Percentage	1.7%	4.4%	22.2%	70.2%	1.5%	100%
Alcohol use in first 3 months of pregnancy						
No	26	79	302	1,214	28	1,649
Percentage	1.6%	4.8%	18.3%	73.6%	1.7%	100
Yes	23	75	307	1,184	36	1625
Percentage	1.4%	4.6%	18.9%	72.9%	2.2%	100
Total	49	154	609	2,398	64	3,274
Percentage	1.5%	4.7%	18.6%	73.2%	2.0%	100
Alcohol use since 4th month of pregnancy						
No	32	102	372	1,482	40	2,028
Percentage	1.6%	5.0%	18.3%	73.1%	2.0%	100%
Yes	17	51	228	891	24	1,211
Percentage	1.4%	4.2%	18.8%	73.6%	2.0%	100%
Total	49	153	600	2,373	64	3,239
Percentage	1.5%	4.7%	18.5%	73.3%	2.0%	100%
Smoking during pregnancy						
No	140	378	2,069	6,383	133	9,103
Percentage	1.5%	4.2%	22.7%	70.1%	1.5%	100%
Yes	40	105	353	1,259	25	1,782
Percentage	2.2%	5.9%	19.8%	70.7%	1.4%	100%
Total	180	483	2,422	7,642	158	10,885
Percentage	1.7%	4.4%	22.3%	70.2%	1.5%	100%

Emp: Employed. Dep: deprived.

Table 70 - Proportion of children in each gestational category by postnatal factors

Characteristics	< 34 weeks	34- 36 weeks	37 – 38 weeks	39-41 weeks	>41 weeks	Total
POSTNATAL FACTORS						
Breastfeeding (ever breastfed)						
Yes	53	129	695	2,076	36	2,989
Percentage	1.8%	4.3%	23.3%	69.5%	1.2%	100%
No	5	40	195	624	14	878
Percentage	0.6%	4.6%	22.2%	71.1%	1.6%	100%
Total	58	169	890	2,700	50	3,867
Percentage	1.5%	4.4%	23.0%	69.8%	1.3%	100%
Maternal anxiety (measured using Generalized Anxiety Disorder 7-item (GAD-7))						
Minimal	70	158	967	2,783	49	4,027
Percentage	1.7%	3.9%	24.0%	69.1%	1.2%	100%
Mild	11	44	205	533	11	804
Percentage	1.4%	5.5%	25.5%	66.3%	1.4%	100%
Moderate	*	16	69	226	*	319
Percentage		5.0%	21.6%	70.9%		100%
Severe	*	14	66	155	*	238
Percentage		5.9%	27.7%	65.1%		100%
Total	86	232	1,307	3,697	66	5,388
Percentage	1.6%	4.3%	24.3%	68.6%	1.2%	100%
Maternal depression (measured using Patient Health Questionnaire-8 (PHQ-8))						
No sig. symptoms	66	148	896	2,628	48	3,786
Percentage	1.7%	3.9%	23.7%	69.4%	1.3%	100%
Mild symptoms	16	45	251	658	13	983
Percentage	1.6%	4.6%	25.5%	66.9%	1.3%	100%
Moderate symptoms	*	21	91	246	*	363
Percentage		5.8%	25.1%	67.8%		100%
Moderately severe and severe	*	18	70	180	*	273
Percentage		6.6%	25.6%	66.0%		100%
Total	86	232	1,308	3,712	67	5,405
Percentage	1.6%	4.3%	24.2%	68.7%	1.2%	100%
DEATH and WITHDRAWALS						
Withdrawals						
Did not withdraw	204	589	2,880	8,999	176	12,848
Percentage	1.6%	4.6%	22.4%	70.0%	1.4%	100%
Withdrew	*	17	70	223	*	324
Percentage		5.3%	21.6%	68.8%		100%
Total	*	606	2,950	9,222	*	13,172
Percentage		4.6%	22.4%	70.0%		100%
Deaths						
Did not die	208	602	2,938	9,192	179	13,119
Percentage	1.6%	4.6%	22.4%	70.1%	1.4%	100%
Died	*	*	12	30	*	53
Percentage			22.6%	56.6%		100%
Total	*	606	2,950	9,222	*	13,172
Percentage		4.6%	22.4%	70.0%		100%

Appendix 4.2.1. Clinical codes – primary care

NB: codes were not reviewed for inclusion in the restricted case ascertainment strategy in they did not appear in any children's records. Therefore, if "appeared in results" = "no", then "included in fully restricted case ascertainment strategy" = "n/a".

[D] = terms defined as 'Symptoms, signs and ill-defined conditions.' [X] = term has a directly equivalent ICD-10 code. NEC = Not Elsewhere Classified (NHS Scotland, 2024)

CTV3 code	CTV3 term	appeared in results	included in fully restricted case ascertainment strategy
Codes relating to cerebral palsy			
Fyu90	[X]Other infantile cerebral palsy	yes	yes
Xab3R	Bilateral spastic cerebral palsy	yes	yes
XE2Q9	Cerebral palsy with spastic diplegia	yes	yes
X00En	Spastic cerebral palsy	yes	yes
XE2Q8	Cerebral palsy	yes	yes
F230z	Congenital diplegia NOS	yes	no
XM03s	Diplegia	yes	no
XaaVK	Gross Motor Function Classification System for Cerebral Palsy level II	yes	no
XE15T	Hemiplegia	yes	no
Xa0fs	Left hemiplegia	yes	no
F243.	Monoplegia of lower limb	yes	no
F244.	Monoplegia of upper limb	yes	no
Xa0fr	Right hemiplegia	yes	no
Xa1kT	Spastic diplegia	yes	no
XE15U	Spastic hemiplegia	yes	no
XaYfK	Spastic hemiplegic cerebral palsy	no	n/a
XaYgp	Spastic quadriplegic cerebral palsy	no	n/a
Y7227	Infantile cerebral palsy NOS	no	n/a
F1370	(Athetoid cerebral palsy) or (Vogt's dis: [ophth][neurol])	no	n/a
P22z.	(Cereb hypopl)(red def brain NOS)([agen][hypopl] brain NEC)	no	n/a
F233.	(Congenital monoplegia) or (congenital spastic foot)	no	n/a
F24yz	(Other paralytic syndromes NOS) or (specified palsy NEC)	no	n/a
XE183	(Paralytic syndromes NOS) or (diplegia) or (monoplegia)	no	n/a
Fyu9.	[X]Cerebral palsy and other paralytic syndromes	no	n/a
Xa0lM	Ataxic cerebral palsy	no	n/a
F23y0	Ataxic infantile cerebral palsy	no	n/a
XE2Q7	Athetoid cerebral palsy	no	n/a
F1371	Athetosis: [double] or [congenital]	no	n/a
F2B2.	Bilateral spastic cerebral palsy	no	n/a
F2Bz.	Cerebral palsy	no	n/a
F232.	Cerebral palsy &/or congenital quadriplegia	no	n/a
XE181	Cerebral palsy (&/or infantile) &/or infantile hemiplegia	no	n/a
F2B..	Cerebral palsy (syn: "CP- Cerebral palsy")	no	n/a

F2By.	Cerebral palsy (synonyms: CP- Cerebral palsy)	no	n/a
F2301	Cerebral palsy with spastic diplegia	no	n/a
X00Eo	Cerebral palsy with spastic tetraparesis	no	n/a
XE2se	Cerebral palsy with spastic tetraplegia	no	n/a
X00Eq	Cerebral palsy with spastic/ataxic diplegia (synonoyms: 'ataxic diplegic ceral palsy'	no	n/a
G669.	Cerebral palsy, not congenital or infantile, acute	no	n/a
XaBE2	Cerebral palsy, not congenital or infantile, acute	no	n/a
F23y6	Choreoathetoid cerebral palsy	no	n/a
XaadE	Choreoathetoid cerebral palsy	no	n/a
X00Ey	Congenital apraxia	no	n/a
XaB4P	Congenital athetosis	no	n/a
XM1Pu	Congenital cerebral palsy	no	n/a
F23..	Congenital cerebral palsy (& spastic)	no	n/a
.F32Z	Congenital cerebral palsy NOS	no	n/a
F23z.	Congenital cerebral palsy NOS	no	n/a
XM1Px	Congenital diplegia	no	n/a
Y6151	Congenital hemiplegia	no	n/a
XE15V	Congenital monoplegia	no	n/a
Xa0lI	Congenital non-progressive ataxia	no	n/a
F2300	Congenital paraplegia	no	n/a
XM1Pw	Congenital quadriplegia	no	n/a
XM1Pv	Congenital spastic cerebral palsy	no	n/a
X00Et	Congenital spastic foot	no	n/a
F242.	Diplegia of upper limbs	no	n/a
XE15M	Double athetosis	no	n/a
X00Ex	Dysequilibrium syndrome (syn DES - dysequilibrium syndrome)	no	n/a
F23y3	Dyskinetic cerebral palsy	no	n/a
X00Eu	Dyskinetic cerebral palsy	no	n/a
X00Ew	Dystonic/rigid cerebral palsy	no	n/a
F220.	Flaccid hemiplegia	no	n/a
F2410	Flaccid paraplegia	no	n/a
F2400	Flaccid tetraplegia	no	n/a
XaaVG	Gross Motor Function Classification System for Cerebral Palsy	no	n/a
XaaVI	Gross Motor Function Classification System for Cerebral Palsy level finding	no	n/a
XaaVJ	Gross Motor Function Classification System for Cerebral Palsy level I (syn: GMFCS for CP level 1)	no	n/a
XaaWD	Gross Motor Function Classification System for Cerebral Palsy level III (synonym: "GMFCS..for cerebral palsy level III")	no	n/a
XaaWE	Gross Motor Function Classification System for Cerebral Palsy level IV (synonym: "GMFCS..for cerebral palsy level IV")	no	n/a
XaaWF	Gross Motor Function Classification System for Cerebral Palsy level V	no	n/a
F22z.	Hemiplegia NOS	no	n/a
F23y1	Hypotonic cerebral palsy	no	n/a
X00Em	Infantile cerebral palsy (synonyms "ICP - infantile cerebral palsy")	no	n/a
F231.	Infantile hemiplegia (syn: 'Hemiplegic cerebral palsy')	no	n/a
X50In	Keratoderma with mental retardation and spastic paraplegia	no	n/a
F222.	Left: [hemiplegia] or [sided weakness]	no	n/a
Y2b6a	Mixed cerebral palsy	no	n/a

XM03p	Monoplegia	no	n/a
F245.	Monoplegia unspecified	no	n/a
X00Es	Monoplegic cerebral palsy affecting lower limb	no	n/a
X00Er	Monoplegic cerebral palsy affecting upper limb	no	n/a
F23y.	Other congenital cerebral palsy	no	n/a
F23yz	Other infantile cerebral palsy NOS	no	n/a
F24..	Other paralytic syndromes	no	n/a
XE15X	Other paralytic syndromes NOS	no	n/a
F24y.	Other specified paralytic syndromes	no	n/a
XM03m	Paralysis	no	n/a
F24z.	Paralysis NOS	no	n/a
1B33.	Paralysis present	no	n/a
Xa3fA	Paralytic syndromes	no	n/a
F241.	Paraplegia	no	n/a
X00Ep	Paraplegia - congenital	no	n/a
F240.	Quadriplegia	no	n/a
XaELO	Residual hemiplegia	no	n/a
F223.	Right: [hemiplegia] or [sided weakness]	no	n/a
F23y2	Spastic cerebral palsy	no	n/a
F2411	Spastic paraplegia	no	n/a
X76je	Spastic quadriplegia	no	n/a
F2401	Spastic tetraplegia	no	n/a
XaB3p	Specified palsy NEC	no	n/a
Motor function problems			
XaO46	[D]Fine motor skills development delay	yes	yes
XaIsc	[D]Gross motor skills development delay	yes	yes
X76q7	Ataxia	yes	yes
XM0qi	Cerebellar ataxia	yes	yes
Y25e1	DCD - developmental coordination disorder	yes	yes
Ub1Th	Developmental verbal dyspraxia	yes	yes
XaXCG	Motor developmental delay	yes	yes
XaKK9	Oculomotor apraxia - Cogan type	yes	yes
X76qF	Truncal ataxia	yes	yes
XaVzu	Apraxia	yes	yes
XE1Z5	Developmental disorder of motor function	yes	yes
XaVzt	Dyspraxia	yes	yes
Xa7PA	Clumsiness	yes	no
XaBBv	Clumsiness -motor delay	yes	no
Xa8Kq	Coordination problem	yes	no
XaItt	Not yet sitting	yes	no
XaIts	Not yet walking	yes	no
29L9.	O/E - clumsy	yes	no
29L8.	O/E - generally unsteady	yes	no
Xa35E	Poor coordination	yes	no
XM0z3	Ataxia	no	n/a
E2F4.	(Aprax, dev) or (clums syn) or (dysprax syn) or (co-ord dis)	no	n/a

R0130	[D]Ataxia NOS	no	n/a
R0132	[D]Dysgraphia	no	n/a
R013z	[D]Incoordination NOS	no	n/a
R013.	[D]Lack of coordination	no	n/a
R0131	[D]Muscular incoordination	no	n/a
Eu82.	[X]Specific developm disord motor funct (& [named variants])	no	n/a
Ub1Ti	Acquired choreiform dyspraxia	no	n/a
XM1MS	Apraxia, developmental	no	n/a
X76q8	Arms ataxic	no	n/a
X76q4	Bumps into things	no	n/a
X75Za	Constructional dyspraxia	no	n/a
Ub1Tg	Developmental articulatory dyspraxia	no	n/a
X76q6	Drops things	no	n/a
X76qC	Dysdiadochokinesis	no	n/a
Xa6tj	Dysdiadochokinesis present	no	n/a
X76qA	Finger-finger test abnormal	no	n/a
X76q9	Finger-nose test abnormal	no	n/a
X76q5	Fumbles with things	no	n/a
X76pr	Gait apraxia	no	n/a
X75ZZ	Gestural apraxia	no	n/a
X76qE	Heel-shin test abnormal	no	n/a
Ub1Tk	Ideational dyspraxia	no	n/a
Ub1Tl	Ideomotor dyspraxia	no	n/a
Xa1bq	Incoordination	no	n/a
XM0z2	Incoordination [D]	no	n/a
XE0rt	Incoordination symptom	no	n/a
1B5Z.	Incoordination symptom NOS	no	n/a
X76qD	Legs ataxic	no	n/a
Xa1br	Muscular incoordination	no	n/a
XaItu	Not yet standing	no	n/a
XM1Wn	O/E - ataxia	no	n/a
29LZ.	O/E - coordination NOS	no	n/a
29L7.	O/E - dysdiadochokinesia present	no	n/a
29L3.	O/E - legs ataxic	no	n/a
29L6.	O/E - past pointing present	no	n/a
Xa867	Oculomotor dyspraxia	no	n/a
Ub1Ta	Oral dyspraxia	no	n/a
XM1Au	Other and unspecified lack of coordination	no	n/a
X76qB	Past pointing	no	n/a
Xa6tl	Past pointing present	no	n/a
XE2bB	Specific developmental disorder of motor function	no	n/a
Xa0to	Speech and language dyspraxias	no	n/a
Ub1To	Tongue tip dyspraxia	no	n/a
Learning disability (intellectual disability)			
Eu7z0	[X]Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour	yes	yes
XaREt	Mild learning disability	yes	yes

XE2a3	Mild mental retardation, IQ in range 50-70	yes	yes
XaQZ3	Moderate learning disability	yes	yes
XaQZ4	Severe learning disability	yes	yes
YA841	Severe learning disability	yes	yes
Xabk1	Significant learning disability	yes	yes
XaaiS	Specific learning disability	yes	yes
E3...	Mental retardation	yes	yes
XaREu	Profound learning disability	yes	yes
ZV400	[V]Problems with learning	yes	no
XacBU	Difficulty comprehending language	yes	no
XaL3Q	Learning disabilities annual health assessment	yes	no
XaJsd	Learning disabilities health action plan completed	yes	no
XaJW9	Learning disabilities health action plan declined	yes	no
XaJW8	Learning disabilities health action plan offered	yes	no
XaJWA	Learning disabilities health action plan reviewed	yes	no
XaJmb	Learning disabilities health assessment	yes	no
XaPx2	Learning disability health examination	yes	no
XaKYb	On learning disability register	yes	no
XaLKE	Seen in learning disabilities clinic	yes	no
E30..	(Mild mental retard (& [feeble-mind][moron])) or (educ subn)	no	n/a
Eu7z.	[X] (Unspec mental retard) or (mental defic [& subnorm] NOS)	no	n/a
Eu700	[X]Mild mental retardation with the statement of no, or minimal, impairment of behaviour	no	n/a
Eu70z	[X]Mild mental retardation without mention of impairment of behaviour	no	n/a
Eu70y	[X]Mild mental retardation, other impairments of behaviour	no	n/a
Eu701	[X]Mild mental retardation, significant impairment of behaviour requiring attention or treatment	no	n/a
Eu71y	[X]Mod retard oth behav impair	no	n/a
Eu710	[X]Moderate mental retardation with the statement of no, or minimal, impairment of behaviour	no	n/a
Eu71z	[X]Moderate mental retardation without mention of impairment of behaviour	no	n/a
Eu711	[X]Moderate mental retardation, significant impairment of behaviour requiring attention or treatment	no	n/a
Eu7y.	[X]Other mental retardation	no	n/a
Eu7y0	[X]Other mental retardation with the statement of no, or minimal, impairment of behaviour	no	n/a
Eu7yz	[X]Other mental retardation without mention of impairment of behaviour	no	n/a
Eu7yy	[X]Other mental retardation, other impairments of behaviour	no	n/a
Eu7y1	[X]Other mental retardation, significant impairment of behaviour requiring attention or treatment	no	n/a
Eu730	[X]Profound mental retardation with the statement of no, or minimal, impairment of behaviour	no	n/a
Eu73z	[X]Profound mental retardation without mention of impairment of behaviour	no	n/a
Eu73y	[X]Profound mental retardation, other impairments of behaviour	no	n/a
Eu731	[X]Profound mental retardation, significant impairment of behaviour requiring attention or treatment	no	n/a
Eu720	[X]Severe mental retardation with the statement of no, or minimal, impairment of behaviour	no	n/a
Eu72z	[X]Severe mental retardation without mention of impairment of behaviour	no	n/a
Eu72y	[X]Severe mental retardation, other impairments of behaviour	no	n/a
Eu721	[X]Severe mental retardation, significant impairment of behaviour requiring attention or treatment	no	n/a

XE1a2	[X]Unspecified mental retardation	no	n/a
Eu7zz	[X]Unspecified mental retardation without mention of impairment of behaviour	no	n/a
Eu7zy	[X]Unspecified mental retardation, other impairments of behaviour	no	n/a
Eu7z1	[X]Unspecified mental retardation, significant impairment of behaviour requiring attention or treatment	no	n/a
X75wy	Below average intellect	no	n/a
Xa1aW	Borderline mental retardation	no	n/a
XaAyZ	Difficulty analysing information	no	n/a
Xa8LF	Difficulty comprehending concept of danger	no	n/a
XacBN	Difficulty comprehending speech	no	n/a
XacBc	Difficulty comprehending written material	no	n/a
XaA3B	Difficulty making considered choices	no	n/a
XaA2O	Difficulty performing logical sequencing	no	n/a
XaAyV	Difficulty processing information	no	n/a
XaA2L	Difficulty reasoning	no	n/a
Xac3m	Difficulty understanding written language	no	n/a
XaA2d	Difficulty using arithmetic reasoning	no	n/a
XaA2T	Difficulty using decision-making strategies	no	n/a
XaA2h	Difficulty using verbal reasoning	no	n/a
XaA2Y	Difficulty using visuospatial reasoning	no	n/a
XacBd	Does comprehend written material	no	n/a
XacBW	Does not comprehend language	no	n/a
XacBP	Does not comprehend speech	no	n/a
XacBe	Does not comprehend written material	no	n/a
Xac3k	Does not understand verbal language	no	n/a
Xac3o	Does not understand written language	no	n/a
X75xn	Impaired ability to learn new material	no	n/a
Ua189	Impaired cognition	no	n/a
XacF6	Intellectual development disorder of unknown aetiology	no	n/a
13Z3.	Intelligence quotient low	no	n/a
XaJW7	Learning disabilities administration status	no	n/a
X75x1	Low intelligence	no	n/a
.6664	Mental handicap problem	no	n/a
6664	Mental handicap problem	no	n/a
E3z..	Mental retardation NOS	no	n/a
XaDki	Mental retardation, congenital heart disease, blepharophimosis, blepharoptosis and hypoplastic teeth	no	n/a
Xaagi	Mild cognitive impairment	no	n/a
Eu816	Mild learning disability	no	n/a
Xaagj	Moderate cognitive impairment	no	n/a
Eu814	Moderate learning disability	no	n/a
.E512	Moderate mental retardation, IQ in range 35-49	no	n/a
E310.	Moderate mental retardation, IQ in range 35-49	no	n/a
Eu71.	Moderate mental retardation, IQ in range 35-49	no	n/a
Xa00k	Moderate mental retardation, IQ in range 35-49	no	n/a
918e.	On learning disability register	no	n/a
Y1642	Other Mental Disability	no	n/a

E31..	Other specified mental retardation	no	n/a
E31z.	Other specified mental retardation NOS	no	n/a
Eu817	Profound learning disability	no	n/a
Y9981	Profound mental retardation	no	n/a
E312.	Profound mental retardation with IQ less than 20	no	n/a
Eu73.	Profound mental retardation with IQ less than 20	no	n/a
Xa01E	Profound mental retardation with IQ less than 20	no	n/a
Xaagk	Severe cognitive impairment	no	n/a
Eu815	Severe learning disability	no	n/a
.E513	Severe mental retardation, IQ in range 20-34	no	n/a
E311.	Severe mental retardation, IQ in range 20-34	no	n/a
Eu72.	Severe mental retardation, IQ in range 20-34	no	n/a
Xa00l	Severe mental retardation, IQ in range 20-34	no	n/a
Ua187	Slow learner	no	n/a
Eu818	Specific learning disability	no	n/a
XaAyY	Unable to analyse information	no	n/a
Xa8LE	Unable to comprehend concept of danger	no	n/a
XaA3A	Unable to make considered choices	no	n/a
XaA2P	Unable to perform logical sequencing	no	n/a
XaAyU	Unable to process information	no	n/a
XaA2K	Unable to reason	no	n/a
XaA2c	Unable to use arithmetic reasoning	no	n/a
XaA2S	Unable to use decision-making strategies	no	n/a
XaA2g	Unable to use verbal reasoning	no	n/a
XaA2X	Unable to use visuospatial reasoning	no	n/a
Special educational needs and disabilities (SEND) and educational difficulty			
X00TL	Developmental disorder of scholastic skill	yes	yes
E2F1.	Dyscalculia	yes	yes
13Z4E	Learning difficulties	yes	yes
E2F2.	Other specific learning difficulty	yes	yes
Eu81z	[X]Developmental disorder of scholastic skills, unspecified	yes	yes
Ub00K	Dyslexia	yes	yes
XaBmg	Difficulty reading	yes	no
XaAzP	Unable to write	yes	no
XaAzQ	Difficulty writing	yes	no
Y1790	Specific arithmetical disorder	no	n/a
XE1bm	(Disturbance in learning) or (development delay - NOS)	no	n/a
XE1bi	(Dyslexia: (& [developmental]) or reading delay	no	n/a
Eu81y	[X]Devel disord scholastic skills: [oth][expressive writing]	no	n/a
XE1a9	[X]Other developmental disorders of scholastic skills	no	n/a
Eu81.	[X]Specific developmental disorders of scholastic skills	no	n/a
Eu812	[X]Specific disorder of arithmetical skills	no	n/a
Eu811	[X]Specific spelling disord (& [retardn, no reading disord])	no	n/a
E2Dy2	Academic underachievement disorder	no	n/a
Xa0tp	Agraphia	no	n/a
E2F01	Alexia	no	n/a

13ZK.	Child with special educational needs	no	n/a
Ub1TD	Deep dysgraphia	no	n/a
Ub1TH	Deep dyslexia	no	n/a
E2F02	Developmental dyslexia	no	n/a
Ub1TC	Dysgraphia	no	n/a
Xa0ER	Educationally subnormal	no	n/a
Ub0ih	Intellectual functioning disability	no	n/a
Eu813	Mixed disorder of scholastic skills	no	n/a
Ub1TG	Paragraphia	no	n/a
Ub1TE	Phonological dysgraphia	no	n/a
Ub1TI	Phonological dyslexia	no	n/a
XaDyv	Provision of special educational needs nursery	no	n/a
E2F00	Reading disorder unspecified	no	n/a
Xa3HI	Severely educationally subnormal	no	n/a
E2F0.	Specific reading disorder	no	n/a
E2F0z	Specific reading disorder NOS	no	n/a
XE1a8	Specific spelling disorder	no	n/a
Ub1TF	Surface dysgraphia	no	n/a
Ub1TJ	Surface dyslexia	no	n/a
XaBmf	Unable to read	no	n/a
Executive function problems			
X75x8	Difficulty making decisions	no	n/a
X75x7	Difficulty making plans	no	n/a
XaCy8	Difficulty processing information accurately	no	n/a
XaCyB	Difficulty processing information at normal speed	no	n/a
X75x5	Difficulty solving problems	no	n/a
Xa2Ve	Impairment of working memory	no	n/a
XaCy7	Unable to process information accurately	no	n/a
XaCyA	Unable to process information at normal speed	no	n/a
Speech, language, and communication disorders			
E2F3.	(Develop disord: [language][speech]) or (articulatn defect)	yes	yes
XaO47	[D]Communication skills development delay	yes	yes
XE1a5	[X]Receptive language disorder	yes	yes
XE1a4	Developmental expressive language disorder	yes	yes
Ub1UQ	Developmental language delay	yes	yes
Ub1UG	Developmental language impairment	yes	yes
XE1a3	Developmental speech articulation disorder	yes	yes
Ub1U0	Developmental speech disorder	yes	yes
XE1Z3	Disorder of speech and language development	yes	yes
Ub1S3	Dysfluency	yes	yes
Ub1UM	Expressive language delay	yes	yes
Ub1UL	Expressive language disorder	yes	yes
Ub1UI	Expressive language impairment	yes	yes
X00TK	Language development disorder	yes	yes
Ub1UH	Language impairment	yes	yes
Ub1U2	Phonological delay	yes	yes

Ub1UO	Receptive language delay	yes	yes
Ub1UJ	Receptive language impairment	yes	yes
Ub1UT	Restricted language development	yes	yes
Ub1UY	Specific language impairment	yes	yes
X00Tb	Speech and language disorder	yes	yes
Ub1U6	Speech delay	yes	yes
Ub0hp	Speech impairment	yes	yes
E2F3z	Speech or language developmental disorder NOS	yes	yes
XE1a7	[X]Developmental disorder of speech and language, unspecified	yes	yes
Ub1UR	Developmental language disorder	yes	yes
Ub1U3	Phonological disorder	yes	yes
ZV401	[V]Problems with communication, including speech	yes	no
XaItr	Not yet speaking	yes	no
XaIUM	O/E - speech delay	yes	no
Ub1UP	Word finding difficulty	yes	no
Eu80y	[X] (Other developmental disorders of speech and language) or (lisping)	no	n/a
Eu80z	[X] Developmental disorder of speech &/or language, unspecified or NOS	no	n/a
XaD2v	Sociolinguistic difficulties	no	n/a
XE1bk	(Developm aphasia) or (delayed speech) or (speech delay)	no	n/a
E2F30	(Developmental aphasia) or (word deafness)	no	n/a
XaKYj	[D]Dysfluency	no	n/a
Eu801	[X] Expressive language disorder: [developmental dysphasia, expressive type] or [developmental aphasia, expressive type]	no	n/a
Eu802	[X] Receptive language disorder (& [congenit auditory imperception] or [development dysphasia, receptive] or [development Wernicke's aphasia] or [word deafness] or [development aphasia, receptive])	no	n/a
Eu800	[X] Specific speech articulation disorder (& [developmental (& phonological)] or [dyslalia] or [functional] or [lalling])	no	n/a
XM19U	[X] Speech disturbances, not elsewhere classified	no	n/a
XE1a6	[X]Other developmental disorders of speech and language	no	n/a
Ub1TL	Anarthria	no	n/a
Ub1Sg	Aphasia	no	n/a
Ub1TZ	Apraxia of speech	no	n/a
Xabxq	Articulatory defect due to conductive hearing loss	no	n/a
Ub1Td	Articulatory dyspraxia	no	n/a
Ub1Uf	Auditory processing disorder	no	n/a
XacFo	Backing of sounds	no	n/a
Ub1TU	Bradyarthria	no	n/a
Ub1Si	Broca's dysphasia	no	n/a
Ub1TQ	Cerebellar dysarthria	no	n/a
XacFq	Cognitive communication disorder	no	n/a
Ub1Sp	Conduction dysphasia	no	n/a
X00F0	Congenital dysarthria	no	n/a
X00F1	Congenital dysphasia	no	n/a
X00F2	Congenital expressive dysphasia	no	n/a
X00F3	Congenital receptive dysphasia	no	n/a
XacFp	De-affrication	no	n/a
Ub1US	Delayed pre-verbal development	no	n/a

XE1Z4	Developmental aphasia	no	n/a
Ub1Tg	Developmental articulatory dyspraxia	no	n/a
Ub1UZ	Developmental dysphasia	no	n/a
XacL0	Developmental language comprehension impairment	no	n/a
Ub1Tf	Developmental motor speech disorder	no	n/a
XacKx	Developmental receptive language impairment	no	n/a
Ub1UX	Developmental semantic impairment	no	n/a
Ub1UW	Developmental syntactic impairment	no	n/a
XaCar	Discourse difficulties	no	n/a
Ub1TM	Dysarthria	no	n/a
Ub1TV	Dysarthria of velopharynx	no	n/a
Ub1TT	Dysarthriapneumophonia	no	n/a
E2F31	Dyslalia	no	n/a
Ub1Tm	Dyspraxia of velopharynx	no	n/a
Ub1Sy	Efferent motor dysphasia	no	n/a
Ub1Sx	Expressive dysphasia	no	n/a
Ub1TR	Extrapyramidal dysarthria	no	n/a
Ub1TO	Flaccid dysarthria	no	n/a
Ub1Sm	Fluent dysphasia	no	n/a
Ub1Sl	Frontal dynamic dysphasia	no	n/a
XacFn	Fronting of sounds	no	n/a
Ub1Sq	Global dysphasia	no	n/a
Ub1T3	Grapheme-phoneme conversion deficit	no	n/a
Ub1Te	Immature articulatory praxis	no	n/a
Ub1U7	Immature sound system	no	n/a
Ub0hr	Impairment of speech form	no	n/a
Ub0hq	Impairment of voice production	no	n/a
Ub1T5	Language disorder associated with right hemisphere damage	no	n/a
Ub1T7	Language disorder associated with thought disorder	no	n/a
Ub1TB	Language-related cognitive disorder	no	n/a
Ub1Ud	Lexical syntactic disorder	no	n/a
Ub1TP	Mixed dysarthria	no	n/a
Ub1Su	Mixed dysphasia	no	n/a
Ub1Sr	Mixed transcortical dysphasia	no	n/a
Ub1TK	Motor speech disorder	no	n/a
Ub1SD	Neurogenic stammering	no	n/a
Ub1UA	Non-contrastive sound system	no	n/a
Ub1Sh	Non-fluent dysphasia	no	n/a
Ub1Tc	Oral-verbal dyspraxia	no	n/a
Ub1T4	Phoneme-grapheme conversion deficit	no	n/a
Ub1U4	Phonological programming deficit	no	n/a
Ub1UK	Phonological syntactic disorder	no	n/a
Ub1St	Posterior dysphasia	no	n/a
Ub1T9	Post-traumatic mutism	no	n/a
Ub1TS	Pyramidal dysarthria	no	n/a
Ub1Sw	Receptive dysphasia	no	n/a

Ub1UU	Restricted expressive language development	no	n/a
Ub1UV	Restricted receptive language development	no	n/a
Ub1U8	Restricted sound system	no	n/a
Ub1Sv	Semantic dysphasia	no	n/a
Ub1T1	Semantic impairment	no	n/a
Ub1Ue	Semantic-pragmatic disorder	no	n/a
Ub1Tt	Semantic-pragmatic impairment	no	n/a
Ub1TN	Spastic dysarthria	no	n/a
XaaaS	Specific speech impairment	no	n/a
Xa0tq	Speech and phonology impairments	no	n/a
Ub1Sz	Subcortical aphasia	no	n/a
Xa4Pz	Syllable deletion	no	n/a
Ub1T0	Syntactic impairment	no	n/a
Ub1Sj	Transcortical motor dysphasia	no	n/a
Ub1So	Transcortical sensory dysphasia	no	n/a
Ub1Tn	Velar dyspraxia	no	n/a
Ub1Tb	Verbal dyspraxia	no	n/a
Attention, impulsivity and hyperactivity (ADHD)			
XE2Q6	Attention deficit hyperactivity disorder	yes	yes
E2E00	Attention deficit without hyperactivity	yes	yes
Eu90z	[X]Hyperkinetic disorder, unspecified	yes	yes
E2E0.	Child attention deficit disorder	yes	yes
E2E..	Childhood hyperkinetic syndrome	yes	yes
XSJK7	Poor concentration	yes	no
X760c	Reduced concentration	yes	no
X760d	Reduced concentration span	yes	no
Ua1XX	Unable to concentrate	yes	no
Eu900	[X]Disturbance of activity and attention	no	n/a
Eu90y	[X]Other hyperkinetic disorders	no	n/a
Eu844	[X]Overactive disorder associated with mental retardation and stereotyped movements	no	n/a
E2E01	Attention deficit hyperactivity disorder	no	n/a
E2E0z	Child attention deficit disorder NOS	no	n/a
Eu902	Deficits in attention motor control and perception	no	n/a
1P00.	Hyperactive behaviour	no	n/a
E2E1.	Hyperkinesis with developmental delay	no	n/a
E2E2.	Hyperkinetic conduct disorder	no	n/a
Eu901	Hyperkinetic conduct disorder	no	n/a
E2Ez.	Hyperkinetic syndrome NOS	no	n/a
E2C3.	Impulse control disorder NEC	no	n/a
E2C3z	Impulse control disorder NOS	no	n/a
E2C30	Impulse control disorder, unspecified	no	n/a
E2Ey.	Other hyperkinetic manifestation	no	n/a
Eu90.	overactive child syndrome	no	n/a
Autism spectrum disorder (ASD)			
XE1aA	[X]Other childhood disintegrative disorder	yes	yes
E1400	Active infantile autism	yes	yes

X00TN	Atypical autism (synonyms: 'atypical autistic syndrome')	yes	yes
X00TM	Autistic spectrum disorder	yes	yes
Y2917	Autistic spectrum disorder - Autism checklist	yes	yes
XE2v2	Childhood autism (synonyms: Kanner's syn, Autistic disorder, Infantile autism, Infantile psychosis	yes	yes
Y2916	Autistic spectrum disorder - Gluten-casein intolerance checklist	no	n/a
Eu84y	[X]Other pervasive developmental disorders	no	n/a
Eu84z	[X]Pervasive developmental disorder, unspecified (syn, autistic spectrum disorder)	no	n/a
E1410	Active disintegrative psychoses	no	n/a
X00TP	Asperger syndrome (synonyms: Schizoid disorder of childhood)	no	n/a
Eu845	Asperger syndrome ~(synonyms: Schizoid disorder of childhood)	no	n/a
Eu841	Atypical autism (syn: Atypical autistic syndrome)	no	n/a
Eu84.	Autistic spectrum disorder (syn: pervasive developmental disoder, autistic continuum, PPD - dervasive developmental disorder)	no	n/a
Ub1Tr	Autistic spectrum disorder (synonocms: pervasive developmental disorder, autistic continuum, PPD - pervasive developmental disorder)	no	n/a
.E2Z3	Autistic spectrum disorder (synonyms: pervasive developmental disorder, autistic continuum, PPD)	no	n/a
E140.	Childhood autism (syn: Kanner's syndrome, autistic disorder, infantile autism, infantile psychosis)	no	n/a
Eu840	Childhood autism (syn: Kanner's syndrome, autistic disorder, infantile autism, infantile psychosis)	no	n/a
E141.	Disintegrative psychosis (synonyms: Heller's syndrome)	no	n/a
E141z	Disintegrative psychosis NOS	no	n/a
Ub1Ts	Idiot savant (synonyms: autistic spectrum disorder with isolated skills)	no	n/a
E140z	Infantile autism NOS	no	n/a
XaesO	Pathological demand avoidance (synonyms: PDA, Newson's syndrome)	no	n/a
Ub1Tw	Persistent developmental avoidance (synonyms: PDA)	no	n/a
E1401	Residual infantile autism	no	n/a
Social, emotional, behavioural problems			
XaO45	[D]Social skills development delay	yes	yes
X00TR	Behavioural and emotional disorder with onset in childhood	yes	yes
Eu931	Childhood phobic anxiety disorder	yes	yes
Eu9y3	Pica of infancy and childhood	yes	yes
Eu9y2	Psychogenic feeding disorder of infancy and childhood	yes	yes
XE1aD	Childhood avoidant disorder [also known as "childhood social anxiety disorder"]	yes	yes
E2C4.	Childhood disorder of conduct and emotion	yes	yes
ZV40.	[V]Mental and behavioural problems	yes	no
ZV403	[V]Other behavioural problems	yes	no
ZV40z	[V]Unspecified mental or behavioural problem	yes	no
X00TT	Adolescent - emotional problem	yes	no
E2C00	Aggressive outburst	yes	no
Xac0T	Behavioural, emotional and social difficulties	yes	no
E2D0z	Disturbance of anxiety and fearfulness in childhood and adolescence NOS	yes	no
Xac0U	Emotional behavioural difficulties	yes	no
X00TU	Childhood conduct disorder	no	n/a
XE1Yv	Childhood emotional disorder	no	n/a
R034C	[D]Social skills development delay	no	n/a
ZV40y	[V]Other specified mental or behavioural problem	no	n/a

ZV404	[V]Pathological sick role	no	n/a
Eu9..	[X]Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
Eu843	[X]Child disinteg dis:[oth][dement infantalis (& named var)]	no	n/a
Eu94z	[X]Childhood disorder of social functioning, unspecified	no	n/a
Eu93z	[X]Childhood emotional disorder, unspecified	no	n/a
Eu910	[X]Conduct disorder confined to the family context	no	n/a
Eu91.	[X]Conduct disorders	no	n/a
Eu8y.	[X]Disord psychological developm: [other] or [devel agnosia]	no	n/a
Eu93.	[X]Emotional disorders with onset specific to childhood	no	n/a
Eu9y.	[X]Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
Eu94y	[X]Other childhood disorders of social functioning	no	n/a
XE1aE	[X]Other childhood emotional disorders	no	n/a
Eu91y	[X]Other conduct disorders	no	n/a
Eu9yy	[X]Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
Eu930	[X]Separation anxiety disorder of childhood	no	n/a
Eu9yz	[X]Unspecified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
E292z	Adjustment reaction with disturbance of other emotion NOS	no	n/a
E292y	Adjustment reaction with mixed disturbance of emotion	no	n/a
E294.	Adjustment reaction with mixed disturbance of emotion and conduct	no	n/a
E292.	Adjustment reaction with predominant disturbance of other emotions	no	n/a
E2C0.	Aggressive unsocial conduct disorder	no	n/a
E2C0z	Aggressive unsocial conduct disorder NOS	no	n/a
Xa1ai	Behavioural disability	no	n/a
XE1Yw	Childhood and adolescence disturbance of unhappiness	no	n/a
XE1Yz	Childhood and adolescent disturbance with introversion	no	n/a
XE1Yx	Childhood and adolescent disturbance with sensitivity	no	n/a
XE1Yy	Childhood and adolescent disturbance with shyness	no	n/a
XE1Z2	Childhood and adolescent emotion disorder NOS	no	n/a
E2D01	Childhood and adolescent fearfulness disturbance	no	n/a
E2D3.	Childhood and adolescent relationship problem	no	n/a
E2D3z	Childhood and adolescent relationship problem NOS	no	n/a
XE1Z1	Childhood and adolescent sensitivity disturbance NOS	no	n/a
E2Dy1	Childhood or adolescent identity disorder	no	n/a
E2D00	Childhood overanxious disorder	no	n/a
Xa1b6	Childhood overanxious disorder	no	n/a
X00TV	Conduct disorder - in family context	no	n/a
E2C2.	Conduct disorder - socialised	no	n/a
Eu911	Conduct disorder - unsocialised	no	n/a
X00TW	Conduct disorder - unsocialised	no	n/a
G56z.	Conduction disorders unspecified	no	n/a
Eu920	Depressive conduct disorder	no	n/a
E2D0.	Disturbance of anxiety and fearfulness in childhood and adolescence	no	n/a
XE1Yr	Disturbance of conduct NEC	no	n/a
E2Czz	Disturbance of conduct NOS	no	n/a
XaLQL	Emotional behaviour disability	no	n/a

E2C23	Group delinquency	no	n/a
E2C34	Intermittent explosive disorder	no	n/a
E2C35	Isolated explosive disorder	no	n/a
E2Cz0	Juvenile delinquency unspecified	no	n/a
E2C4z	Mixed disturbance of conduct and emotion NOS	no	n/a
Eu92z	Mixed disturbance of conduct and emotion NOS	no	n/a
E2C40	Neurotic delinquency	no	n/a
XE1Ys	Nonaggressive unsocial conduct disorder	no	n/a
E2C1z	Nonaggressive unsocial conduct disorder NOS	no	n/a
E2755	Non-organic infant feeding disturbance	no	n/a
E2Dy0	Oppositional defiant disorder	no	n/a
Eu913	Oppositional defiant disorder	no	n/a
E2Dy.	Other childhood and adolescent emotional problems	no	n/a
E2Dyz	Other childhood and adolescent emotional problems NOS	no	n/a
E2Cy.	Other conduct disturbances	no	n/a
E2Cyz	Other conduct disturbances NOS	no	n/a
E2920	Separation anxiety disorder	no	n/a
E2D30	Sibling jealousy	no	n/a
XE2bC	Sibling rivalry disorder	no	n/a
E2C20	Socialised childhood truancy	no	n/a
E2C2z	Socialised conduct disorder NOS	no	n/a
XE1Yt	Unsocial childhood truancy	no	n/a
E2Cz.	Unspecified disturbance of conduct	no	n/a
Feeding problems			
R033.	[D]Feeding difficulties and mismanagement	yes	no
R033z	[D]Feeding difficulties NOS	yes	no
R0330	[D]Feeding problem in infant	yes	no
XSJFL	Feeding problem in child	yes	no
163Z.	Feeding problem NOS	yes	no
163..	Feeding problem symptom	yes	no
XaaxT	Acquired chewing difficulty	no	n/a
193Z.	Chewing symptom NOS	no	n/a
193..	Chewing symptoms	no	n/a
XaaxN	Developmental chewing difficulty	no	n/a
XacSD	Developmental delay in feeding	no	n/a
XabAP	Developmental dysphagia	no	n/a
1932.	Difficulty chewing	no	n/a
Xa4KF	Difficulty sucking	no	n/a
Xa4JG	Does not chew	no	n/a
Xa4KE	Does not suck	no	n/a
Xa4JE	Unable to chew	no	n/a
Xa4KC	Unable to suck	no	n/a
Sleep apnoea			
XaEGP	[D]Sleep apnoea syndrome	yes	no
X0084	Obstructive sleep apnoea	yes	no
X0083	Sleep apnoea	yes	no

XE2nU	[D]Hypersomnia with sleep apnoea	no	n/a
R0051	[D]Insomnia with sleep apnoea	no	n/a
X0087	Alveolar sleep apnoea	no	n/a
X0085	Central sleep apnoea	no	n/a
X0086	Mixed sleep apnoea	no	n/a
Visual impairment			
F491.	Better eye: low vision, Lesser eye: profound visual impairment	yes	yes
XM19P	Blind left eye	yes	yes
XaYiO	Mild visual impairment	yes	yes
XE16M	Visual loss NOS	yes	yes
F493.	Visual loss, both eyes unqualified	yes	yes
Xa1Ih	Partial sight	yes	yes
XE16L	Visual impairment	yes	yes
F496.	Low vision, one eye	yes	no
F49..	Impaired vision (& [blindness &/or low] or [partial sight])	no	n/a
P356.	(Specified optic disc anomalies) or (optic disc congenital anomalies)	no	n/a
F49z.	(Visual loss NOS) or (acquired blindness)	no	n/a
FyuL0	[X]Other disorders of binocular vision	no	n/a
FyuJ2	[X]Other disorders of optic nerve and visual pathways in diseases classified elsewhere	no	n/a
FyuL1	[X]Other visual disturbances	no	n/a
FyuL.	[X]Visual disturbances and blindness	no	n/a
F4915	Better eye: moderate visual impairment, Lesser eye: blind, unspecified	no	n/a
F4923	Better eye: moderate visual impairment, Lesser eye: low vision unspecified	no	n/a
F4925	Better eye: moderate visual impairment, Lesser eye: moderate visual impairment	no	n/a
F4917	Better eye: moderate visual impairment, Lesser eye: near total visual impairment	no	n/a
F4918	Better eye: moderate visual impairment, Lesser eye: profound visual impairment	no	n/a
F4924	Better eye: moderate visual impairment, Lesser eye: severe visual impairment	no	n/a
F4916	Better eye: moderate visual impairment, Lesser eye: total visual impairment	no	n/a
F4904	Better eye: near total visual impairment, Lesser eye: near total visual impairment	no	n/a
F4903	Better eye: near total visual impairment, Lesser eye: total visual impairment	no	n/a
F4902	Better eye: near total visual impairment, Lesser eye: unspecified	no	n/a
F4907	Better eye: profound visual impairment, Lesser eye: near total visual impairment	no	n/a
F4908	Better eye: profound visual impairment, Lesser eye: profound visual impairment	no	n/a
F4906	Better eye: profound visual impairment, Lesser eye: total visual impairment	no	n/a
F4905	Better eye: profound visual impairment, Lesser eye: unspecified	no	n/a
F4911	Better eye: severe visual impairment, Lesser eye: blind, unspecified	no	n/a
F4921	Better eye: severe visual impairment, Lesser eye: low vision unspecified	no	n/a
F4913	Better eye: severe visual impairment, Lesser eye: near total visual impairment	no	n/a
F4914	Better eye: severe visual impairment, Lesser eye: profound visual impairment	no	n/a
F4922	Better eye: severe visual impairment, Lesser eye: severe visual impairment	no	n/a
F4912	Better eye: severe visual impairment, Lesser eye: total visual impairment	no	n/a
XE191	Blind or low vision - both eyes	no	n/a

XE193	Blind or low vision - one eye only	no	n/a
XM19Q	Blind right eye	no	n/a
1B75.	Blindness	no	n/a
F490.	Blindness - both eyes	no	n/a
F490z	Blindness both eyes NOS	no	n/a
XE195	Blindness or low vision NOS	no	n/a
Ua1f0	Blindness, monocular	no	n/a
F4950	Blindness, one eye, unspecified	no	n/a
F4901	Both eyes total visual impairment	no	n/a
XaYPJ	Combined visual and hearing impairment	no	n/a
F4H73	Cortical blindness	no	n/a
X75bS	Dim vision	no	n/a
F494.	Legal blindness USA	no	n/a
F4965	Lesser eye: moderate visual impairment, Better eye: near normal vision	no	n/a
F4966	Lesser eye: moderate visual impairment, Better eye: normal vision	no	n/a
F4964	Lesser eye: moderate visual impairment, Better eye: unspecified	no	n/a
F4955	Lesser eye: near total visual impairment, Better eye: near normal vision	no	n/a
F4956	Lesser eye: near total visual impairment, Better eye: normal vision	no	n/a
F4954	Lesser eye: near total visual impairment, Better eye: unspecified	no	n/a
F4958	Lesser eye: profound visual impairment, Better eye: near normal vision	no	n/a
F4959	Lesser eye: profound visual impairment, Better eye: normal vision	no	n/a
F4957	Lesser eye: profound visual impairment, Better eye: unspecified	no	n/a
F4962	Lesser eye: severe visual impairment, Better eye: near normal vision	no	n/a
F4963	Lesser eye: severe visual impairment, Better eye: normal vision	no	n/a
F4961	Lesser eye: severe visual impairment, Better eye: unspecified	no	n/a
F4952	Lesser eye: total visual impairment, Better eye: near normal vision	no	n/a
F4953	Lesser eye: total visual impairment, Better eye: normal vision	no	n/a
F4951	Lesser eye: total visual impairment, Better eye: unspecified	no	n/a
F492.	Low vision, both eyes	no	n/a
F492z	Low vision, both eyes NOS	no	n/a
F4920	Low vision, both eyes unspecified	no	n/a
F496z	Low vision, one eye NOS	no	n/a
F4960	Low vision, one eye, unspecified	no	n/a
XaYiP	Mild binocular visual impairment	no	n/a
XaYfH	Moderate binocular visual impairment	no	n/a
XaYfI	Moderate monocular visual impairment	no	n/a
F4910	One eye blind, one eye low vision	no	n/a
F491z	One eye blind, one eye low vision NOS	no	n/a
Ua1ez	Painful blind eye	no	n/a
X00gP	Partial sight - both eyes	no	n/a
F495z	Profound impairment one eye NOS	no	n/a
F495.	Profound impairment, one eye	no	n/a
X74UF	Provision for visual and hearing impairment	no	n/a
X74UH	Provision of communicator for visual and hearing impairment	no	n/a
X74UG	Provision of guide help for visual and hearing impairment	no	n/a
XaYfF	Severe binocular visual impairment	no	n/a

XaYfG	Severe monocular visual impairment	no	n/a
F4900	Unspecified blindness both eyes	no	n/a
F49y.	Visual loss, one eye, unqualified	no	n/a
X75bQ	Weak vision	no	n/a
Hearing impairment			
F592.	Mixed conductive and sensorineural hearing loss	yes	yes
F5921	Mixed conductive and sensorineural hearing loss, bilateral	yes	yes
F5920	Mixed conductive and sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side	yes	yes
F5916	Sensorineural hearing loss, bilateral	yes	yes
XaaLg	Bilateral congenital sensorineural hearing loss	yes	yes
1C133	Bilateral deafness	yes	yes
F5914	Congenital sensorineural deafness	yes	yes
X00kQ	Low frequency deafness	yes	yes
XaZuA	Moderate sensorineural hearing loss	yes	yes
XE17N	Sensorineural hearing loss	yes	yes
XaZuB	Severe sensorineural hearing loss	yes	yes
1C131	Unilateral deafness	yes	yes
XM0Cb	Deafness symptom	yes	no
XaAw3	Ability to hear voice abnormal	no	n/a
XaaLf	Bilateral profound sensorineural hearing loss	no	n/a
X00kO	Chronic deafness	no	n/a
F5911	Cochlear hearing loss	no	n/a
F591y	Combined perceptive hearing loss	no	n/a
XaRE1	Congenital prelingual deafness	no	n/a
X75qM	Dead ear	no	n/a
1C13.	Deafness (& symptom)	no	n/a
X00kR	Dominant sensorineural hearing loss	no	n/a
XM1QG	Drug ototoxicity - deafness	no	n/a
Xa7SL	Hearing for conversational voice impaired	no	n/a
Xa7SN	Hearing for loud voice impaired	no	n/a
Xa7SP	Hearing for voice impaired	no	n/a
Xa7SJ	Hearing for whisper impaired	no	n/a
F59..	Hearing loss (& [deafness])	no	n/a
X00kX	Hearing loss associated with syndrome	no	n/a
X00kP	High frequency deafness	no	n/a
F5843	Impaired auditory discrimination	no	n/a
XaOPs	Maternally inherited deafness	no	n/a
XE17O	Ototoxicity - deafness	no	n/a
F5915	Ototoxicity - deafness (& [drug])	no	n/a
1C132	Partial deafness	no	n/a
F591z	Perceptive hearing loss NOS	no	n/a
X00kU	Perinatal sensorineural hearing loss	no	n/a
X00kV	Postnatal acquired sensorineural hearing loss	no	n/a
X00kT	Recessive sensorineural hearing loss	no	n/a
F591.	Sensorineural hearing loss (& [deafness: [high frequency] or [low frequency])	no	n/a

F5917	Sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side	no	n/a
XaAw5	Unable to hear conversational voice	no	n/a
XaAw6	Unable to hear loud voice	no	n/a
XaAw4	Unable to hear whisper	no	n/a
F5910	Unspecified perceptive hearing loss	no	n/a
F5912	Neural hearing loss	no	n/a
XaZuE	Profound sensorineural hearing loss	no	n/a
Developmental delay			
XaX18	[X]Neurodevelopmental delay	yes	yes
Xa40J	Development delay NOS	yes	yes
Ua14s	Global developmental delay	yes	yes
E2Fy.	Other development delays	yes	yes
X76B7	Developmental delay	yes	yes
E2F..	Specific delays in development	yes	yes
R0340	[D]Delayed milestone	yes	no
XM1AI	Delayed milestone	yes	no
XaLTp	Not yet toilet trained	yes	no
Y05ac	Toileting problems	yes	no
XE1bg	Developmental delay (& [learning] or [specific])	no	n/a
XE1hA	O/E - delayed milestones	no	n/a
General developmental disorder (unclassifiable)			
X00TI	Developmental disorder	yes	yes
E2Fz.	Developmental disorder NOS	yes	yes
Ub1S4	Developmental dysfluency	yes	yes
E2F5.	Mixed disorder of psychological development	yes	yes
Eu8..	Disorder of psychological development	yes	yes
13VCZ	Disability NOS	yes	no
13VC5	Registered disabled	yes	no
Y2344	Developmental Problem	yes	no
9EB4.	DLA 370 Disability living allowance completed	yes	no
XE1gX	[D]Failure in development NOS	no	n/a
R03z.	[D]Nutritional, metabolic or developmental symptoms NOS	no	n/a
ZV402	[V]Other mental problems	no	n/a
Eu83.	[X]Mixed specific developmental disorders	no	n/a
XE1aB	[X]Other disorders of psychological development	no	n/a
Eu8z.	[X]Unspecified disorder of psychological development	no	n/a
13VC3	Chronic physical disability	no	n/a
Y3288	Development exam result: Unsatisfactory	no	n/a
Y6312	Development, failure in [D]	no	n/a
XM0zA	Development, failure in [D]	no	n/a
X00TQ	Developmental agnosia	no	n/a
Ub0q0	Developmental therapy	no	n/a
13VC1	Disability - moderate	no	n/a
13VC2	Disability - severe	no	n/a
XabmM	Early childhood developmental disability	no	n/a
XacF5	Early childhood developmental disability of unknown aetiology	no	n/a

Y6723	Failure in development NOS [D]	no	n/a
XaQk5	History of developmental disorder	no	n/a
6972	Mobility allowance medical	no	n/a
6665	Physical handicap problem	no	n/a
XM1AJ	Physiological development failure	no	n/a
Excluded codes: breastfeeding codes, or not developmental disorders as per NICE			
62P1.	Breast fed	yes	n/a
62P5.	Breast-feeding started	yes	n/a
62P6.	Breast-feeding stopped	yes	n/a
62P3.	Breast-feeding with supplement	yes	n/a
62PA.	Mother currently breast-feeding	yes	n/a
Q4332	Breast milk jaundice	yes	n/a
Q433A	Breast milk jaundice	yes	n/a
XaPO8	Breastfeeding and supplementary bottle feeding at discharge from hospital	yes	n/a
XaPO0	Breastfeeding at discharge from hospital	yes	n/a
X76Nh	Milk leaking from breast	yes	n/a
62PB.	Bottle changed to breast	no	n/a
71385	Expression of breast milk	no	n/a
Xa3GM	Advice to change breast milk intake	no	n/a
Ua1IY	Applying expressed breast milk to nipples	no	n/a
Y1381	Breast and Bottle (Non Breast Milk)	no	n/a
Ub0HY	Breast milk	no	n/a
Ub0AD	Breast milk intake	no	n/a
X76Ne	Breast milk observation	no	n/a
Y1380	Breast Milk Only	no	n/a
X76fF	Breast milk stool	no	n/a
XaX2G	Breastfeeding assessment	no	n/a
XaY6u	Breastfeeding support offered	no	n/a
Ub0HZ	Expressed breast milk	no	n/a
Ua1IV	Expressing colostrum	no	n/a
Ua1JX	Giving expressed breast milk	no	n/a
Xa4k2	Inadequate flow of breast milk	no	n/a
X76Ng	Observation of flow of breast milk	no	n/a
X005S	Rett syndrome	yes	n/a
Xa6te	Observation of coordination	yes	n/a
X006o	Acquired epileptic aphasia	yes	n/a
E27z2	Lisping	yes	n/a
.N721	Down's syndrome	yes	n/a
64P..	(Child exam.: development exam) or (motor develop.- child)	yes	n/a
64...	(Child health care)(inf feed meth)(breast/oth feed diff age)	yes	n/a
R034y	[D]Other specified failure of physiological development	yes	n/a
PyuA5	[X]Other variants of Turner's syndrome	yes	n/a
F4865	Abnormal rod or cone threshold	yes	n/a
X00gD	Accommodative insufficiency	yes	n/a
Xa9BU	Amblyopia	yes	n/a
F4803	Ametropic amblyopia	yes	n/a

PKyz5	Angelman's syndrome	yes	n/a
F472.	Astigmatism	yes	n/a
F472z	Astigmatism NOS	yes	n/a
XE16K	Blurred vision NOS	yes	n/a
1C22.	Buzzing in ear	yes	n/a
9O6..	Child development check admin	yes	n/a
XaXUH	Child examination for emotional development	yes	n/a
XE2tn	Child examination.: development	yes	n/a
64PZ.	Child examination.: development NOS	yes	n/a
64P2.	Child examination.: fine motor devel.	yes	n/a
64P4.	Child examination.: language develop.	yes	n/a
64P1.	Child examination.:gross motor devel.	yes	n/a
64P3.	Child examination.:social development	yes	n/a
XaIt3	Child examination: gait development	yes	n/a
XaLTq	Children's hearing screening	yes	n/a
XaYQ0	Chromosome 22q11 deletion syndrome	yes	n/a
F485.	Colour blindness	yes	n/a
P3560	Congenital optic disc coloboma	yes	n/a
X00e4	Congenital stationary night blindness	yes	n/a
Y0812	Crowded LogMar visual assessment	yes	n/a
Xa3Eb	Delayed visual maturation	yes	n/a
PJz2.	Deletion of chromosome NOS	yes	n/a
Ub1ve	Demand fed	yes	n/a
C3911	DiGeorge syndrome	yes	n/a
F482.	Diplopia	yes	n/a
Xa874	Disorder of optic disc	yes	n/a
XE16v	Disorder of optic nerve and visual pathway	yes	n/a
F4Hz.	Disorder of optic nerve or visual pathway NOS	yes	n/a
X75q9	Distressed by loud noise	yes	n/a
X75by	Double vision in one eye	yes	n/a
X75bx	Double vision with both eyes open	yes	n/a
XE1MZ	Down's syndrome	yes	n/a
PJ0z.	Down's syndrome NOS	yes	n/a
X78Ek	Down's syndrome NOS	yes	n/a
F4H20	Drusen of optic disc	yes	n/a
PJyy2	Fragile X chromosome	yes	n/a
X78FB	Fragile X syndrome	yes	n/a
X76Az	General development	yes	n/a
X76B2	General physical development	yes	n/a
Xa09f	Growth delay	yes	n/a
X75bT	Hazy vision	yes	n/a
X77Ga	Hearing change	yes	n/a
1C1..	Hearing symptoms	yes	n/a
F5842	Hyperacusis	yes	n/a
F470.	Hypermetropia	yes	n/a
X008X	Hypoplasia of optic disc	yes	n/a

X00g6	Index myopia	yes	n/a
X78F8	Karyotype 47, XYY	yes	n/a
Q437z	Kernicterus of newborn NOS	yes	n/a
PJ7..	Klinefelter's syndrome	yes	n/a
PKy1.	Laurence-Moon-Biedl syndrome	yes	n/a
XM1W8	Motor develop.- child	yes	n/a
XaNWy	Mowat-Wilson syndrome	yes	n/a
F471.	Myopia	yes	n/a
XaKc9	Neonatal hearing test	yes	n/a
Y01b3	Neurodevelopmental functional observation	yes	n/a
F486.	Night blindness	yes	n/a
F486z	Night blindness NOS	yes	n/a
1C2..	Noises in ear	yes	n/a
F4H1.	Optic atrophy	yes	n/a
X78ak	Optic nerve glioma	yes	n/a
F4H3.	Optic neuritis	yes	n/a
XaE6b	Optic neuropathy	yes	n/a
PJ33z	Other deletion of part of a chromosome NOS	yes	n/a
PJ33.	Other deletions of part of a chromosome	yes	n/a
F4H6.	Other visual pathway disorder	yes	n/a
F4H0.	Papilloedema	yes	n/a
F4H01	Papilloedema due to raised intracranial pressure	yes	n/a
PJ02.	Partial trisomy 21 in Down's syndrome	yes	n/a
X78El	Partial trisomy 21 in Down's syndrome	yes	n/a
X00Ej	Periventricular leucomalacia	yes	n/a
PKy93	Prader-Willi syndrome	yes	n/a
XaXEm	Referral to child development centre	yes	n/a
Y05a7	Referral to child development centre	yes	n/a
8HT6.	Referral to developmental clinic	yes	n/a
F4220	Retinopathy of prematurity	yes	n/a
Eu842	Rett syndrome	yes	n/a
1C23.	Ringing in ear	yes	n/a
XaIPY	Scotopic sensitivity	yes	n/a
Y1769	Seen by child development centre	yes	n/a
XaLKD	Seen in child development centre	yes	n/a
9N0P.	Seen in developmental clinic	yes	n/a
X008Y	Septo-optic dysplasia	yes	n/a
X00g3	Simple myopia	yes	n/a
F4752	Spasm of accommodation	yes	n/a
XE1Jy	Specified optic disc anomalies	yes	n/a
F4801	Strabismic amblyopia	yes	n/a
X008W	Tilted optic disc	yes	n/a
1C2Z.	Tinnitus symptom NOS	yes	n/a
PJ0..	Trisomy 21- meiotic nondisjunction	yes	n/a
PJ00.	Trisomy 21- meiotic nondisjunction	yes	n/a
PJ01.	Trisomy 21- mitotic nondisjunction mosaicism	yes	n/a

PJ63.	Turner's syndrome	yes	n/a
XE1Mf	Turner's syndrome NOS	yes	n/a
XE16H	Unspecified amblyopia	yes	n/a
F4720	Unspecified astigmatism	yes	n/a
F4H7.	Visual cortex disorder	yes	n/a
SJ03.	Visual cortex injury	yes	n/a
F48..	Visual disturbance	yes	n/a
F1371	double athetosis	no	n/a
F230.	Congenital diplegia	no	n/a
X00gN	Acquired blindness	no	n/a
XaE6s	Acquired blindness, both eyes	no	n/a
XaE6t	Acquired blindness, one eye	no	n/a
XaE6t	Acquired blindness, one eye	no	n/a
XaF9A	Drug induced optic neuropathy	no	n/a
XaPen	Impaired vision due to diabetic retinopathy	no	n/a
XacBM	Able to comprehend speech	no	n/a
XE0pf	Relative - mental handicap	no	n/a
E1411	Residual disintegrative psychoses	no	n/a
F234.	Infantile hemiplegia NOS	no	n/a
XaeUO	Locked in syndrome	no	n/a
XaNWb	Worster-Drought syndrome	no	n/a
1BL..	Loss of judgement	no	n/a
Xa6tk	Dysdiadochokinesis absent	no	n/a
Ub1Tj	Mixed acquired dyspraxia	no	n/a
XE1hw	O/E - coordination	no	n/a
Xa6tf	Observation of pattern of coordination	no	n/a
XabxE	Acquired dysarthria	no	n/a
Xa0tr	acquired dysphasias	no	n/a
XacKz	Acquired language comprehension impairment	no	n/a
Ub1Sf	Acquired language disorder	no	n/a
XacKv	Acquired receptive language impairment	no	n/a
Ub1Sk	Anomia	no	n/a
Ub1Ss	Anterior dysphasia	no	n/a
Xabxp	Articulatory defect secondary to dental defect	no	n/a
Ub1Ua	Congenital auditory imperception	no	n/a
Ub1T6	Language disorder of dementia	no	n/a
Ub1U9	Limited sound system	no	n/a
Ub1Sn	Wernicke's dysphasia	no	n/a
XaF1F	Inflammatory papillitis	no	n/a
XE1OW	(Gonadal dysgenesis (& Turner)) or Turner's syndrome	no	n/a
PKy0.	(Multi syst cong anom NEC) or (Prader-Willi) or (Noonan syn)	no	n/a
XE1OY	(Patau's syndrome) or (Klinefelter's syndrome)	no	n/a
PJ63z	(Turner syn NOS) or (Bonn-Ullr syn NOS) or (Ovar dwarf NEC)	no	n/a
PJ37.	(Whole chrom monosomy: [variants]) or (autosom delet mosaic)	no	n/a
R0331	[D]Feeding problem in elderly	no	n/a
XaL2A	[X]Cocktail party syndrome	no	n/a

Ryu75	[X]Lack of expected normal physiological development, unspecified	no	n/a
FyuJ0	[X]Optic atrophy in diseases classified elsewhere	no	n/a
FyuU2	[X]Other abnormal auditory perceptions	no	n/a
PyuA2	[X]Other deletions from the autosomes	no	n/a
PyuA1	[X]Other deletions of part of a chromosome	no	n/a
FyuK4	[X]Other disorders of refraction	no	n/a
Ryu74	[X]Other lack of expected normal physiological development	no	n/a
PyuA7	[X]Other male with 46,XX karyotype	no	n/a
Qyu57	[X]Other specified kernicterus	no	n/a
PyuA6	[X]Other specified sex chromosome abnormalities, female phenotype	no	n/a
PyuA8	[X]Other specified sex chromosome abnormalities, male phenotype	no	n/a
FyuJ1	[X]Retrobulbar neuritis in diseases classified elsewhere	no	n/a
PyuAA	[X]Sex chromosome abnormality, male phenotype, unspecified	no	n/a
ZVu0P	[X]Special screening examination for certain developmental disorders in childhood	no	n/a
FyuM2	[X]Visual disturbances in diseases classified elsewhere	no	n/a
XaYQ3	10q partial trisomy syndrome	no	n/a
XSDcM	11q partial monosomy syndrome	no	n/a
XaYQe	15q partial trisomy syndrome	no	n/a
XaYQU	4p partial trisomy syndrome	no	n/a
XaYQb	9p partial trisomy syndrome	no	n/a
X00kE	Abnormal auditory perception	no	n/a
F4867	Abnormal dark adaptive curve NOS	no	n/a
F475z	Accommodation disorder NOS	no	n/a
XaEJ8	Accommodative fatigue	no	n/a
XaEJ9	Accommodative inertia	no	n/a
F4816	Accommodative strain	no	n/a
F4854	Acquired colour blindness	no	n/a
F4864	Acquired night blindness	no	n/a
F4H32	Acute retrobulbar neuritis	no	n/a
PJy0.	Additional sex chromosome	no	n/a
Xa0Yy	Alpha thalassaemia-mental retardation syndrome	no	n/a
F480.	Amblyopia ex anopsia	no	n/a
F480z	Amblyopia ex anopsia NOS	no	n/a
F4800	Amblyopia: [unspecified] or [congenital]	no	n/a
X50Hu	Amelocerebrohypohidrotic syndrome	no	n/a
F4731	Aniseikonia	no	n/a
F4730	Anisometropia	no	n/a
F473.	Anisometropia and aniseikonia	no	n/a
F473z	Anisometropia or aniseikonia NOS	no	n/a
X00gK	Anisometropic amblyopia	no	n/a
PJ30.	Antimongolism syndrome	no	n/a
X008g	Arteritic ischaemic optic neuropathy	no	n/a
X78Et	Autosomal deletion - mosaicism	no	n/a
X008l	Autosomal dominant optic atrophy	no	n/a
X008v	Avulsion of optic nerve	no	n/a
X00g0	Axial hypermetropia	no	n/a

X78al	Benign tumour of optic nerve and sheath	no	n/a
X75pv	Binaural diplacusis	no	n/a
X00e8	Blue cone monochromatism	no	n/a
X75qR	Bone conduction better than air	no	n/a
X78Ez	Bonnevie-Ullrich syndrome NOS	no	n/a
Xa0Zb	Borjeson-Forssman-Lehmann syndrome	no	n/a
X00kY	Cat eye syndrome	no	n/a
9O6Z.	Child develop. check admin.NOS	no	n/a
XaYIf	Child visual perception assessment	no	n/a
XaYQ1	Chromosome 3p deletion syndrome	no	n/a
XaYQ2	Chromosome 4q deletion syndrome	no	n/a
XE1Ma	Chromosome replaced with ring or dicentric	no	n/a
PKy61	Cockayne syndrome	no	n/a
X50HX	Coffin-Siris syndrome	no	n/a
X7AG5	Colostrum sample	no	n/a
F485z	Colour blindness NOS	no	n/a
X75oK	Complete optic atrophy	no	n/a
X0093	Compression of optic chiasm	no	n/a
X009D	Compression of optic radiation	no	n/a
X0098	Compression of optic tract	no	n/a
X009F	Compression of visual cortex	no	n/a
XaE6D	Compressive optic atrophy	no	n/a
XaEVg	Compressive optic neuropathy	no	n/a
XaYOy	Congenital amblyopia	no	n/a
X00Ee	Congenital and developmental anomalies of the nervous system	no	n/a
X00g5	Congenital axial myopia	no	n/a
X00gL	Congenital colour blindness	no	n/a
F4863	Congenital night blindness NOS	no	n/a
X008R	Congenital optic disc anomaly	no	n/a
Y1862	Cover Test - Fail	no	n/a
Y0814	Cover test - No deviation near and distance	no	n/a
Y0816	Cover test - No deviation near and distance - limited exam	no	n/a
Y0815	Cover test - No deviation near. Distance testing not possible	no	n/a
Y081a	Cover test - Small esophoria near and distance. Well compensated	no	n/a
Y0819	Cover test - Small esophoria near. Well compensated. No deviation for distance	no	n/a
Y0818	Cover test - Small exophoria near and distance. Well compensated	no	n/a
Y0817	Cover test - Small exophoria near. Well compensated. No deviation for distance	no	n/a
Y081b	Cover test - Test indicates result sufficiently abnormal to warrant referral	no	n/a
Y4953	Cover test fail	no	n/a
F4H21	Crater-like optic disc holes	no	n/a
PJ31.	Cri du chat syndrome	no	n/a
X00g1	Curvature hypermetropia	no	n/a
X00gE	Cycloplegic paralysis of accommodation	no	n/a
F4866	Delayed rod or cone adaption	no	n/a
PJ331	Deletion of arm of chromosome 18: [long] or [p]	no	n/a

PJ332	Deletion of arm of chromosome 18: [q] or [short]	no	n/a
PJ330	Deletion of long arm of chromosome 13	no	n/a
XE2ac	Deletion of long arm of chromosome 18	no	n/a
X78Eu	Deletion of part of autosome	no	n/a
XE2ad	Deletion of short arm of chromosome 18	no	n/a
PJ32.	Deletion of short arm of chromosome 4	no	n/a
PJ34.	Deletion seen only at prometaphase	no	n/a
XM1FU	Deletion with complex rearrangement	no	n/a
PJ35.	Deletions with other complex rearrangements	no	n/a
F4851	Deutan defect	no	n/a
X008t	Diabetes insipidus, diabetes mellitus, optic atrophy and deafness	no	n/a
F5841	Diplacusis	no	n/a
XaJmd	Discharge from learning disability team	no	n/a
F475.	Disorder of accommodation	no	n/a
F4H51	Disorder of optic chiasm due to non-pituitary neoplasm	no	n/a
F4H50	Disorder of optic chiasm due to pituitary disorder	no	n/a
F4H52	Disorder of optic chiasm due to vascular disorder	no	n/a
X00fv	Disorder of refraction	no	n/a
F47..	Disorder of refraction and accommodation	no	n/a
F4H..	Disorders of optic nerve &/or visual pathways	no	n/a
X75pu	Distorted hearing	no	n/a
Xa7SD	Does not attend to direct verbal communication	no	n/a
XaCKc	Down's screening blood test abnormal	no	n/a
XaXOz	Down's syndrome antenatal screening information leaflet given	no	n/a
PJ2..	Edwards' syndrome	no	n/a
X78Em	Edward's syndrome NOS	no	n/a
XM1KI	Family - [Downs/Mongol child]	no	n/a
X78F5	Female with 46 XY karyotype	no	n/a
X78F3	Female with more than three X chromosomes	no	n/a
XaDjY	Floating-Harbor syndrome	no	n/a
F4H04	Foster-Kennedy syndrome	no	n/a
X78FC	FRAXA	no	n/a
X78FD	FRAXE	no	n/a
XaYOw	Functional amblyopia	no	n/a
X00gG	Functional paralysis of accommodation	no	n/a
XaEEm	Functional visual loss	no	n/a
F4H14	Glaucomatous optic atrophy	no	n/a
F4862	Hereditary night blindness NOS	no	n/a
P2xz1	Hereditary optic atrophy	no	n/a
XE16x	Hereditary optic atrophy NOS	no	n/a
XE16x	Hereditary optic atrophy NOS	no	n/a
X77O1	Heteronymous diplopia	no	n/a
1C24.	Hissing in ear	no	n/a
X77O0	Homonymous diplopia	no	n/a
XaE6C	Idiopathic optic disc swelling	no	n/a
XaPen	Impaired vision due to diabetic retinopathy	no	n/a

X77O3	Incongruous diplopia	no	n/a
X75qL	Inconsistent results on voice testing	no	n/a
X00g2	Index hypermetropia	no	n/a
Xa9Bf	Infarction of optic chiasm	no	n/a
X009B	Infarction of optic radiation	no	n/a
X0096	Infarction of optic tract	no	n/a
Xa9Bg	Infarction of visual cortex	no	n/a
X00gF	Infective paralysis of accommodation	no	n/a
XaE6E	Infiltrative optic neuropathy	no	n/a
F4H53	Inflammatory disorder of optic chiasm	no	n/a
X009A	Inflammatory disorder of optic radiation	no	n/a
F4H62	Inflammatory disorder of optic tract	no	n/a
F4H72	Inflammatory disorder of visual cortex	no	n/a
XaE6B	Inherited optic neuropathy	no	n/a
X0092	Injury of optic chiasm	no	n/a
X009C	Injury of optic radiation	no	n/a
X0097	Injury of optic tract	no	n/a
X00gJ	Internal ophthalmoplegia	no	n/a
F4722	Irregular astigmatism	no	n/a
X00g9	Irregular astigmatism - corneal	no	n/a
X00gA	Irregular astigmatism - lenticular	no	n/a
Y2473	Is/are parent(s) anxious about childs speech/language development?	no	n/a
F4H40	Ischaemic optic neuropathy	no	n/a
PJ631	Karyotype 45, X	no	n/a
PJ632	Karyotype 46, X iso (Xq)	no	n/a
PJ633	Karyotype 46, X with abnormal sex chromosome except iso (Xq)	no	n/a
PJy2.	Karyotype 47, XXX	no	n/a
Q4370	Kernicterus	no	n/a
XE1g1	Kernicterus (& [due to isoimmunisation])	no	n/a
Q424.	Kernicterus due to isoimmunisation	no	n/a
Q437.	Kernicterus not due to isoimmunisation	no	n/a
Y0811	Keystone Chart Assessment	no	n/a
XaYYN	Kleefstra syndrome	no	n/a
PJ71.	Klinefelter syndr: [male, more than 2 X chrom][XXXY][XXXXY]	no	n/a
PJ72.	Klinefelter's syndrome - male with 46 XX karyotype	no	n/a
XE1Mg	Klinefelter's syndrome - male with more than two X chromosomes	no	n/a
PJ7z.	Klinefelter's syndrome NOS	no	n/a
XM1MK	Klinefelter's syndrome XXXXY	no	n/a
XM1MJ	Klinefelter's syndrome XXXY	no	n/a
PJ73.	Klinefelter's syndrome, XXYY	no	n/a
PJ74.	Klinefelter's syndrome, XY/XXY mosaic	no	n/a
X00Eg	Late secondary abnormalities of the central nervous system	no	n/a
X00fx	Latent hypermetropia	no	n/a
X75qT	Lateralisation of sound	no	n/a
X00e1	Laurence-Moon syndrome	no	n/a
F4H16	Leber's hereditary optic neuropathy	no	n/a

F4H16	Leber's hereditary optic neuropathy	no	n/a
Y2614	Listening and attention skills	no	n/a
Xa7SH	Localisation of voice impaired	no	n/a
X75qK	Loss of discrimination on voice testing	no	n/a
F5844	Loudness recruitment	no	n/a
XaL2v	Lujan-Fryns syndrome	no	n/a
XaEEl	Macular displacement	no	n/a
PJ510	Major partial trisomy	no	n/a
X78F7	Male with 46, XX karyotype	no	n/a
X78FA	Male with sex chromosome mosaicism	no	n/a
X78F9	Male with structurally abnormal sex chromosome	no	n/a
X78ah	Malignant astrocytoma of optic nerve	no	n/a
X78aj	Malignant meningioma of optic nerve sheath	no	n/a
F4021	Malignant myopia	no	n/a
X78ag	Malignant tumour of optic nerve	no	n/a
X78af	Malignant tumour of optic nerve and sheath	no	n/a
X78ai	Malignant tumour of optic nerve sheath	no	n/a
X00fy	Manifest hypermetropia	no	n/a
4I2A.	Maternal milk sample	no	n/a
X78an	Melanocytoma of optic nerve head	no	n/a
X78am	Meningioma of optic nerve sheath	no	n/a
A36y0	Meningococcal optic neuritis	no	n/a
PKy92	Menkes syndrome	no	n/a
X78kz	Metastasis to optic nerve	no	n/a
PJ60.	Mixed gonadal dysgenesis	no	n/a
Xa0PV	Monaural diplacusis	no	n/a
F4853	Monochromatism	no	n/a
PJ3z.	Monosomies and deletions from the autosomes NOS	no	n/a
PJ370	Monosomy 21, mosaicism	no	n/a
PJ3..	Monosomy and deletion from autosome	no	n/a
PJy13	Mosaic including XXXXY	no	n/a
PJy11	Mosaic XO/XX	no	n/a
PJy10	Mosaic XO/XY	no	n/a
PJy12	Mosaic XY/XXY	no	n/a
X78F4	Mosaicism - lines with various numbers of X chromosomes	no	n/a
PJ635	Mosaicism 45, X / other cell line with abnormal sex chromosome	no	n/a
Xa9D6	Mosaicism 45, X; 46, XX	no	n/a
X78F1	Mosaicism 45, X; 46, XY	no	n/a
X00Eh	Multicystic encephalomalacia	no	n/a
XE1Ml	Multiple system congenital anomalies NEC	no	n/a
Y05c2	Night bags	no	n/a
X75qS	No difference in air or bone conduction	no	n/a
X008h	Non-arteritic ischaemic optic neuropathy	no	n/a
PKy80	Noonan's syndrome	no	n/a
Ub1S5	Normal non-fluency	no	n/a
X40Xn	Nutritional mental retardation	no	n/a

F4H33	Nutritional optic neuropathy	no	n/a
X00kL	Obscure auditory dysfunction	no	n/a
X75qF	Observation of ability to hear voice	no	n/a
X75qN	Observation of conductivity of sound	no	n/a
Xa7Rv	Observation of tinnitus	no	n/a
F4861	Oguchi's disease	no	n/a
F4H1z	Optic atrophy NOS	no	n/a
X008q	Optic atrophy secondary to papilloedema	no	n/a
F4H13	Optic atrophy secondary to retinal disease	no	n/a
F4H5.	Optic chiasm disorder	no	n/a
F4H5z	Optic chiasm disorder NOS	no	n/a
SJ01.	Optic chiasm injury	no	n/a
X75oW	Optic disc drusen - buried	no	n/a
X75oV	Optic disc drusen - elevated	no	n/a
X75oC	Optic disc vascular anomaly	no	n/a
XE19T	Optic nerve &/or visual path disorders	no	n/a
SJ0..	Optic nerve and pathway injury	no	n/a
F4H42	Optic nerve compression	no	n/a
SJ00.	Optic nerve injury	no	n/a
XE1o4	Optic nerve or pathway injury NOS	no	n/a
F4H41	Optic nerve sheath haemorrhage	no	n/a
XE19X	Optic neuritis &/or retrobulbar neuritis	no	n/a
F4H3z	Optic neuritis NOS	no	n/a
XaFav	Optic neuroretinitis	no	n/a
SJ02.	Optic pathway injury	no	n/a
X0099	Optic radiation disorder	no	n/a
X0094	Optic tract disorder	no	n/a
F584.	Other abnormal auditory perception	no	n/a
F584z	Other abnormal auditory perception NOS	no	n/a
FyuK1	Other and unspecified heterotropia	no	n/a
PJ3y.	Other deletions from the autosomes	no	n/a
F481B	Other metamorphopsia	no	n/a
F4H2z	Other optic disc disorder NOS	no	n/a
F4H2.	Other optic disc disorders	no	n/a
F4H4z	Other optic nerve disorder NOS	no	n/a
F4H4.	Other optic nerve disorders	no	n/a
F481L	Other psychophysical visual disturbance	no	n/a
F47y.	Other refraction and accommodation disorders	no	n/a
F47yz	Other refraction or accommodation disorder NOS	no	n/a
Y2617	Other skill difficulties	no	n/a
XE1Mm	Other specified anomalies NOS	no	n/a
F24y.	Other specified paralytic syndromes	no	n/a
F48y.	Other specified visual disturbance	no	n/a
F48yz	Other specified visual disturbance NOS	no	n/a
PJ50y	Other specified whole chromosome trisomy syndrome	no	n/a
F4814	Other transient visual loss	no	n/a

F4818	Other visual discomfort	no	n/a
F481G	Other visual distortion	no	n/a
F4H6z	Other visual pathway disorder NOS	no	n/a
X78Ey	Ovarian dwarfism NEC	no	n/a
XSDcU	Pallister-Killian syndrome	no	n/a
F4H31	Papillitis	no	n/a
F4H02	Papilloedema due to low ocular pressure	no	n/a
F4H03	Papilloedema due to retinal disorder	no	n/a
F4H0z	Papilloedema NOS	no	n/a
Xa0PW	Paracusis	no	n/a
Xa0PY	Paracusis Willisii	no	n/a
X77O2	Paradoxical diplopia	no	n/a
F4750	Paralysis of accommodation	no	n/a
X77sz	Partial hypoplasia of optic disc	no	n/a
XE16w	Partial optic atrophy	no	n/a
X78Ep	Partial trisomy 13 in Patau's syndrome	no	n/a
X78En	Partial trisomy 18 in Edward's syndrome	no	n/a
PJ1..	Patau's syndrome	no	n/a
X78Eo	Patau's syndrome NOS	no	n/a
X00fz	Pathological hypermetropia	no	n/a
X00g4	Pathological myopia	no	n/a
X00gI	Pharmacological paralysis of accommodation	no	n/a
F481C	Photopsia	no	n/a
X008Z	Pit of optic disc	no	n/a
Y2615	Play skills	no	n/a
PJ524	Polyploidy	no	n/a
X008s	Post-compressive optic atrophy	no	n/a
F4H12	Post-inflammatory optic atrophy	no	n/a
F5801	Presbyacusis	no	n/a
XE1AH	Presbyacusis (& [senile &/or other])	no	n/a
F474.	Presbyopia	no	n/a
F4H11	Primary optic atrophy	no	n/a
F4850	Protan defect	no	n/a
F4H23	Pseudopapilloedema	no	n/a
X008w	Radiation damage to optic nerve	no	n/a
XE18t	Refraction &/or accommodation disorders	no	n/a
F47z.	Refraction or accommodation disorder NOS	no	n/a
F481E	Refractive diplopia	no	n/a
F481F	Refractive polyopia	no	n/a
F4721	Regular astigmatism	no	n/a
X00g7	Regular astigmatism - corneal	no	n/a
X00g8	Regular astigmatism - lenticular	no	n/a
X008e	Retrobulbar neuritis	no	n/a
X00e7	Rod monochromatism	no	n/a
Xa0ZS	Schprintzen	no	n/a
X77t0	Sectorial hypoplasia of optic disc	no	n/a

X75pw	Sensitive hearing	no	n/a
X78Ex	Sex chromosome abnormality - female phenotype	no	n/a
X78F6	Sex chromosome abnormality - male phenotype	no	n/a
PJy1.	Sex chromosome mosaicism	no	n/a
PJy1z	Sex chromosome mosaicism NOS	no	n/a
X00mm	Shprintzen syndrome	no	n/a
X00fw	Simple hypermetropia	no	n/a
Y2616	Skills in the fluency of speech	no	n/a
XaIwZ	Smith-Magenis syndrome	no	n/a
Xa0LP	Sound lateralised to affected ear	no	n/a
Xa0LQ	Sound lateralised to non-affected ear	no	n/a
Xa0LR	Sound perceived in midline	no	n/a
X75px	Sounds are very loud	no	n/a
P356z	Specified optic disc anomaly NOS	no	n/a
X77Gd	Speech discrimination score	no	n/a
X75q8	Startle response to sound	no	n/a
X00El	Status marmoratus	no	n/a
F4802	Stimulus deprivation amblyopia	no	n/a
XaX5J	Structural central nervous system abnormality	no	n/a
F481z	Subjective visual disturbance NOS	no	n/a
F481.	Subjective visual disturbances	no	n/a
F4811	Sudden visual loss	no	n/a
XaJJM	Suspected Downs syndrome	no	n/a
F4751	Total internal ophthalmoplegia	no	n/a
F4H34	Toxic optic neuropathy	no	n/a
X00gH	Toxic paralysis of accommodation	no	n/a
F47y1	Toxic refraction or accommodation disorder	no	n/a
X00gB	Toxic refractive disorder	no	n/a
F47y0	Transient refractive change	no	n/a
X008x	Traumatic optic neuropathy	no	n/a
PJ523	Triploidy	no	n/a
PJ504	Trisomy 10	no	n/a
PJ506	Trisomy 12	no	n/a
PJ11.	Trisomy 13 - mitotic nondisjunction mosaicism	no	n/a
PJ10.	Trisomy 13, meiotic nondisjunction	no	n/a
PJ20.	Trisomy 18 - meiotic nondisjunction	no	n/a
PJ21.	Trisomy 18 - mitotic nondisjunction mosaicism	no	n/a
PJ508	Trisomy 22	no	n/a
PJ501	Trisomy 7	no	n/a
PJ502	Trisomy 8	no	n/a
PJ503	Trisomy 9	no	n/a
F4852	Tritan defect	no	n/a
X0090	Tumour of optic nerve	no	n/a
X78F2	Turner's phenotype - ring chromosome karyotype	no	n/a
PJ630	Turner's phenotype, karyotype normal	no	n/a
PJ634	Turner's phenotype, mosaicism 45, X; 46, XX or 45, X; 46, XY	no	n/a

XE1Me	Turner's phenotype, other variant karyotypes	no	n/a
X78F0	Turner's phenotype, partial X deletion karyotype	no	n/a
PJ636	Turner's phenotype: [variant karyotypes]	no	n/a
P244.	Ulegyria	no	n/a
PKyz0	Ullrich-Feichtiger syndrome, chimaera	no	n/a
Xaaa7	Ulnar mammary syndrome	no	n/a
Y0813	Uncrowded LogMar visual assessment	no	n/a
F4860	Unspecified night blindness	no	n/a
F4H10	Unspecified optic atrophy	no	n/a
F4H30	Unspecified optic neuritis	no	n/a
F5840	Unspecified other abnormal auditory perception	no	n/a
F4H00	Unspecified papilloedema	no	n/a
F4810	Unspecified subjective visual disturbance	no	n/a
F4H70	Visual cortex disorder due to neoplasm	no	n/a
F4H71	Visual cortex disorder due to vascular disorder	no	n/a
F4H7z	Visual cortex disorder NOS	no	n/a
F48z.	Visual disturbance NOS	no	n/a
F4H60	Visual pathway disorder due to neoplasm	no	n/a
F4H61	Visual pathway disorder due to vascular disorder	no	n/a
C245.	Vitamin A deficiency with night blindness	no	n/a
Xa0Ze	Weaver syndrome	no	n/a
XSGQj	Weber's test - sound lateralised to left	no	n/a
XSGQi	Weber's test - sound lateralised to right	no	n/a
XSGQh	Weber's test - sound perceived in midline	no	n/a
PJ36.	Whole chromosome monosomy - meiotic nondisjunction	no	n/a
XE2R1	Whole chromosome monosomy - mitotic nondisjunction mosaicism	no	n/a
PJ37z	Whole chromosome monosomy, mosaicism NOS	no	n/a
PJ50.	Whole chromosome trisomy syndrome	no	n/a
PJ50z	Whole chromosome trisomy syndrome NOS	no	n/a
PJ50w	Whole chromosome trisomy, meitotic nondisjunction	no	n/a
PJ50x	Whole chromosome trisomy, mosaicism	no	n/a
PKy4.	William syndrome	no	n/a
X00kS	X-linked sensorineural hearing loss	no	n/a
PJ70.	XXY Klinefelter's syndrome	no	n/a
PJy3.	XXY Klinefelter's syndrome	no	n/a
PJ640	XY, female phenotype	no	n/a
PKy94	Zellweger's syndrome	no	n/a
1C12.	Hearing difficulty	yes	n/a
XE0s9	Hearing loss	yes	n/a
Xa7SQ	Hearing problem	yes	n/a
1C1Z.	Hearing symptom NOS	yes	n/a
Xa1Ip	Hearing worse	yes	n/a
XaZuF	Mild sensorineural hearing loss	yes	n/a
F59y.	Other specified forms of hearing loss	yes	n/a
XaIxM	Difficulty hearing with background noise	yes	n/a
Xa7S7	No response to high frequency sounds	no	n/a

Xa7S9	No response to low frequency sounds	no	n/a
Xa7S5	No response to sound	no	n/a
Xa0PN	Postoperative profound sensorineural hearing loss	no	n/a
X75qQ	Air conduction better than bone	no	n/a
Xa0PZ	Difficulty hearing in noise	no	n/a
XaIxN	Difficulty hearing whispers	no	n/a
Xa08C	Primary sleep apnoea of newborn	no	n/a
Ub1T2	Acoustic analysis deficit	no	n/a
X75pz	Observation of response to sound	no	n/a
XaAvY	Rinne false negative	no	n/a
1C25.	Roaring in ear	no	n/a
Y10a2	School Entrant Hearing Screening - Incomplete - behavioural issues	no	n/a
Y108f	School Entrant Hearing Screening - Left Ear - No Clear Response	no	n/a
Y109e	School Entrant Hearing Screening - No clear response - bilateral referral	no	n/a
Y109d	School Entrant Hearing Screening - No clear response - unilateral referral	no	n/a
Y108d	School Entrant Hearing Screening - Right Ear - No Clear Response	no	n/a
X75qJ	Voice testing inconclusive	no	n/a
XaFo1	Deteriorating hearing	no	n/a

Appendix 4.2.2. Clinical codes – secondary care

NB: codes were not reviewed for inclusion in the restricted case ascertainment strategy in they did not appear in any children's records. Therefore, if "appeared in results" = "no", then "included in fully restricted case ascertainment strategy" = "n/a"

code	ICD-10 term	appeared in results	included in fully restricted case ascertainment strategy
Cerebral palsy			
G80.0	Spastic quadriplegic cerebral palsy	yes	yes
G80.2	Spastic hemiplegic cerebral palsy	yes	yes
G80.8	Other cerebral palsy	yes	yes
G80.9	Cerebral Palsy, unspecified	yes	yes
G83.0	Diplegia of upper limb	yes	yes
G80.1	Spastic diplegic cerebral palsy	yes	yes
G81.9	Hemiplegia unspecified	yes	no
G82.4	Spastic tetraplegia	yes	no
G82.5	Tetraplegia unspecified/quadriplegia NOS	yes	no
G83.3	Monoplegia unspecified	yes	no
G83.9	Paralytic syndrome, unspecified	yes	no
G80	Cerebral palsy	no	n/a
G80.3	Dyskinetic cerebral palsy	no	n/a
G80.4	Ataxic cerebral palsy	no	n/a
G81	Hemiplegia	no	n/a
G81.0	Flaccid hemiplegia	no	n/a
G81.1	Spastic hemiplegia	no	n/a
G82	Paraplegia and tetraplegia	no	n/a
G82.0	Flaccid paraplegia	no	n/a
G82.1	Spastic paraplegia	no	n/a
G82.2	Paraplegia	no	n/a
G82.3	Flaccid tetraplegia	no	n/a
G83	other paralytic syndromes	no	n/a
G83.1	Monoplegia of lower limb	no	n/a
G83.2	Monoplegia of upper limb	no	n/a
G83.5	Locked-in syndrome	no	n/a
Motor function problems			
F82	Specific developmental disorder of motor function	yes	yes
R27.0	Ataxia, unspecified	yes	yes
R27.8	Other and unspecified lack of coordination	yes	no
R27	Other lack of coordination	no	n/a
Learning disability (intellectual disability)			
F70.0	With the statement of no, or minimal, impairment of behaviour	yes	yes
F70.9	Without mention of impairment of behaviour	yes	yes
F71.9	Without mention of impairment of behaviour	yes	yes
F72.1	Significant impairment of behaviour requiring attention or treatment	yes	yes
F72.9	Without mention of impairment of behaviour	yes	yes

F73.9	Without mention of impairment of behaviour	yes	yes
F79.1	Significant impairment of behaviour requiring attention or treatment	yes	yes
F79.8	Other impairments of behaviour	yes	yes
F79.9	Without mention of impairment of behaviour	yes	yes
F06.7	Mild cognitive disorder	no	n/a
F70	Mild mental retardation	no	n/a
F70.1	Significant impairment of behaviour requiring attention or treatment	no	n/a
F70.8	Other impairments of behaviour	no	n/a
F71	Moderate mental retardation	no	n/a
F71.0	With the statement of no, or minimal, impairment of behaviour	no	n/a
F71.1	Significant impairment of behaviour requiring attention or treatment	no	n/a
F71.8	Other impairments of behaviour	no	n/a
F72	Severe mental retardation	no	n/a
F72.0	With the statement of no, or minimal, impairment of behaviour	no	n/a
F72.8	Other impairments of behaviour	no	n/a
F73	Profound mental retardation	no	n/a
F73.0	With the statement of no, or minimal, impairment of behaviour	no	n/a
F73.1	Significant impairment of behaviour requiring attention or treatment	no	n/a
F73.8	Other impairments of behaviour	no	n/a
F78	Other mental retardation	no	n/a
F78.0	With the statement of no, or minimal, impairment of behaviour	no	n/a
F78.1	Significant impairment of behaviour requiring attention or treatment	no	n/a
F78.8	Other impairments of behaviour	no	n/a
F78.9	Without mention of impairment of behaviour	no	n/a
F79	Unspecified mental retardation	no	n/a
F79.0	With the statement of no, or minimal, impairment of behaviour	no	n/a
R41.8	Other and unspecified symptoms and signs involving cognitive functions and awareness [NB – this was originally coded as executive function, but recoded as learning disability]	yes	no
special educational needs and disabilities (SEND) and educational difficulty			
F81.9	Developmental disorder of scholastic skills, unspecified	yes	yes
F81.0	Specific reading disorder	yes	yes
F81.1	Specific spelling disorder	yes	yes
Z55.0	Illiteracy and low-level literacy	yes	no
Z55.4	Educational maladjustment and discord with teachers and classmates	yes	no
Z55.8	Other problems related to education and literacy	yes	no
F81	Specific developmental disorders of scholastic skills	no	n/a
F81.2	Specific disorder of arithmetical skills	no	n/a
F81.3	Mixed disorder of scholastic skills	no	n/a
F81.8	Other developmental disorders of scholastic skills	no	n/a
Z55	Problems related to education and literacy	no	n/a
Z55.1	Schooling unavailable and unattainable	no	n/a
Z55.2	Failed examinations	no	n/a
Z55.3	Underachievement in school	no	n/a
Z55.9	Problem related to education and literacy, unspecified	no	n/a

speech, language, and communication disorders			
F98.5	Stuttering [stammering]	yes	yes
F80	Specific speech articulation disorder	yes	no
F80.9	Developmental disorder of speech and language, unspecified	yes	no
F80.1	Expressive language disorder	no	n/a
F80.2	Receptive language disorder	no	n/a
F80.3	Acquired aphasia with epilepsy [Landau-Kleffner]	no	n/a
F80.8	Other developmental disorders of speech and language	no	n/a
F98.6	Cluttering	no	n/a
F90.0	Disturbance of activity and attention - [inc. ADHD]	yes	yes
F90.9	Hyperkinetic disorder, unspecified	yes	yes
F84.4	Overactive disorder associated with mental retardation and stereotyped movements	no	n/a
F90	Hyperkinetic disorders	no	n/a
F90.1	Hyperkinetic conduct disorder	no	n/a
F90.8	Other hyperkinetic disorders	no	n/a
Autism Spectrum Disorder (ASD)			
F84.0	Childhood autism	yes	yes
F84.1	Atypical autism	yes	yes
F84.9	Pervasive developmental disorder, unspecified	yes	yes
F84	Pervasive developmental disorders	no	n/a
F84.3	Other childhood disintegrative disorder	no	n/a
F84.5	Asperger's syndrome	no	n/a
F84.8	Other pervasive developmental disorders	no	n/a
social, emotional, behavioural problems			
F91.8	Other conduct disorders	yes	yes
F91.9	Conduct disorder, unspecified	yes	yes
F93.8	Other childhood emotional disorders	yes	yes
F94.0	Elective mutism	yes	yes
F94.9	Childhood disorder of social functioning, unspecified	yes	yes
F95.2	Combined vocal and multiple motor tic disorder [de la Tourette]	yes	yes
F95.8	Other tic disorders	yes	yes
F95.9	Tic disorder, unspecified	yes	yes
F98.3	Pica of infancy and childhood	yes	yes
R45.1	Restlessness and agitation	yes	no
R45.4	Irritability and anger	yes	no
R45.6	Physical violence	yes	no
R45.8	Other symptoms and signs involving emotional state	yes	no
F91	Conduct disorders	no	n/a
F91.0	Conduct disorder confined to the family context	no	n/a
F91.1	Unsocialized conduct disorder	no	n/a
F91.2	Socialized conduct disorder	no	n/a
F91.3	Oppositional defiant disorder	no	n/a
F92	Mixed disorders of conduct and emotions	no	n/a
F92.0	Depressive conduct disorder	no	n/a
F92.8	Other mixed disorders of conduct and emotions	no	n/a
F92.9	Mixed disorder of conduct and emotions, unspecified	no	n/a

F93	Emotional disorders with onset specific to childhood	no	n/a
F93.0	Separation anxiety disorder of childhood	no	n/a
F93.1	Phobic anxiety disorder of childhood	no	n/a
F93.2	Social anxiety disorder of childhood	no	n/a
F93.3	Sibling rivalry disorder	no	n/a
F93.9	Childhood emotional disorder, unspecified	no	n/a
F94	Disorders of social functioning with onset specific to childhood and adolescence	no	n/a
F94.1	Reactive attachment disorder of childhood	no	n/a
F94.2	Disinhibited attachment disorder of childhood	no	n/a
F94.8	Other childhood disorders of social functioning	no	n/a
F95	Tic disorders	no	n/a
F95.1	Chronic motor or vocal tic disorder	no	n/a
F98	Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
F98.4	Stereotyped movement disorders	no	n/a
F98.8	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
F98.9	Unspecified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	no	n/a
R45	Symptoms and signs involving emotional state	no	n/a
R45.0	Nervousness	no	n/a
R45.2	Unhappiness	no	n/a
R45.3	Demoralization and apathy	no	n/a
R45.5	Hostility	no	n/a
R45.7	State of emotional shock and stress, unspecified	no	n/a
feeding problems			
F98.2	Feeding disorder of infancy and childhood	yes	no
R63.3	Feeding difficulties and mismanagement	yes	no
sleep apnoea			
G47.3	Sleep apnoea	yes	no
visual impairment			
H54.0	Blindness, binocular	yes	yes
H54.1	Severe visual impairment, binocular	yes	yes
H54.4	Blindness, monocular	yes	yes
H54.5	Severe visual impairment, monocular	yes	yes
H54.7	Unspecified visual loss	yes	yes
H53.4	Visual field defects	yes	no
H54.9	Unspecified visual impairment (binocular)	yes	no
H54	Visual impairment including blindness (binocular or monocular)	no	n/a
H54.2	Moderate visual impairment, binocular	no	n/a
H54.6	Moderate visual impairment, monocular	no	n/a
hearing impairment			
H90.3	Sensorineural hearing loss, bilateral	yes	yes
H90.4	Sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side	yes	yes
H90.5	Sensorineural hearing loss, unspecified	yes	yes
H90.6	Mixed conductive and sensorineural hearing loss, bilateral	yes	yes
H90.7	Mixed conductive and sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side	yes	yes

H90	Conductive and sensorineural hearing loss	no	n/a
H90.8	Mixed conductive and sensorineural hearing loss, unspecified	no	n/a
developmental delay			
F98.0	Nonorganic enuresis	yes	no
F98.1	Nonorganic encopresis	yes	no
R62.9	Lack of expected normal physiologic development unspec	yes	no
R620	Delayed milestone	yes	no
general developmental disorder (unclassifiable)			
F88	Other disorders of psychological development	yes	yes
F89	Unspecified disorder of psychological development	yes	yes
F83	Mixed specific developmental disorders	yes	no
Not a developmental disorder as per NICE			
F84.2	Rett syndrome	yes	n/a
G83.8	Other specified paralytic syndromes	yes	n/a
P28.4	Other apnoea of newborn	yes	n/a
H53.0	Amblyopia ex anopsia	yes	n/a
H53.1	Subjective visual disturbances	yes	n/a
H53.2	Diplopia	yes	n/a
H53.8	Other visual disturbances	yes	n/a
H53.9	Visual disturbance, unspecified	yes	n/a
G83.4	Cauda equina syndrome	yes	n/a
R638	Other symptoms & signs concerning food & fluid intake	yes	n/a
H91.1	Presbycusis	no	n/a
H93.3	Disorders of acoustic nerve	no	n/a
P28.3	Primary sleep apnoea of newborn	no	n/a
H53	Visual disturbances	no	n/a
H53.3	Other disorders of binocular vision	no	n/a
H53.5	Colour vision deficiencies	no	n/a
H53.6	Night blindness	no	n/a
H54.3	Mild or no visual impairment, binocular	no	n/a
H91.3	Deaf mutism, not elsewhere classified	no	n/a
R62.8	Other lack of expected normal physiological development	yes	n/a
H90.1	Conductive hearing loss, unilateral with unrestricted hearing on the contralateral side	yes	n/a
H91.9	Hearing loss, unspecified	yes	n/a
H90.0	Conductive hearing loss, bilateral	yes	n/a
H90.2	Conductive hearing loss, unspecified	yes	n/a
H91.2	Sudden idiopathic hearing loss	yes	n/a
H91.8	Other specified hearing loss	yes	n/a
H91	Other hearing loss	no	n/a
H91.0	Ototoxic hearing loss	no	n/a

Appendix 5.1. Characteristics of the cohort dichotomised by outcome – developmental disorders from medical records

Table 71 – Neonatal characteristics by developmental disorder (from medical records) by 12th birthday

	no developmental disorder	developmental disorder	total
Gestational Age Category χ2 35.3; p <0.001			
< 34 weeks	169	45	214
Percentage	79.0%	21.0%	100%
34 - 36 weeks	517	89	606
Percentage	85.3%	14.7%	100%
37 - 38 weeks	2,591	359	2,950
Percentage	87.8%	12.2%	100%
39 - 41 weeks	8,244	978	9,222
Percentage	89.4%	10.6%	100%
>41 weeks	154	26	180
Percentage	85.6%	14.4%	100%
Total	11,675	1,497	13,172
Percentage	88.6%	11.4%	100%
Child's Sex χ2 162.52; p <0.001			
Male	5,796	1,005	6,801
Percentage	85.2%	14.8%	100.0
Female	5,879	492	6,371
Percentage	92.3%	7.7%	100%
Total	11,675	1,497	13,172
Percentage	88.6%	11.4%	100%
Multiplicity χ2 0.06; p = 0.8			
Singleton	11,406	1,461	12,867
Percentage	88.7%	11.4%	100%
Twins	269	36	305
Percentage	88.2%	11.8%	100%
Total	11,675	1,497	13,172
Percentage	88.6%	11.4%	100%
Small for gestational age (SGA) χ2 6.63; p = 0.01			
Not SGA	9,842	1,225	11,067
Percentage	88.9%	11.1%	100%
SGA	1,559	236	1,795
Percentage	86.9%	13.2%	100%
Total	11,401	1,461	12,862
Percentage	88.6%	11.4%	100%

Table 72 - Antenatal characteristics by developmental disorder (from medical records) by 12th birthday

	no developmental disorder	**developmental disorder**	**total**
Mother's age at child's birth T: 0.07; p: 0.9			
Mean	27.5	27.5	27.5
SD	5.6	5.9	5.6
Median	27	27	27
Range	15-45	15-49	15-49
n	11,675	1,497	13,172
Pre-eclampsia χ2 0.06; p: 0.8			
absent Percent	10,856 88.7%	1,384 11.3%	12,240 100%
present Percent	301 88.3%	40 11.7%	341 100%
Total Percent	11,157 88.7%	1,424 11.3%	12,581 100%
Gestational Diabetes χ2 1.73; p: 0.2			
absent Percent	10,682 88.8%	1,353 11.2%	12,035 100%
present Percent	917 87.4%	132 12.6%	1,049 100%
Total Percent	11,599 88.7%	1,485 11.4%	13,084 100%

Table 73 – Socio demographic characteristics and ethnicity by developmental disorder (from medical records) by 12th birthday

	no developmental disorder	developmental disorder	total
Socio-economic position: 5 group latent class (measured during pregnancy) χ2: 26.0; p <0.001			
Least deprived, most educated	1,909	187	2,096
Percentage	91.1%	8.9%	100%
Employed, not materially deprived	1,936	224	2,160
Percentage	89.6%	10.4%	100%
Employed, no access to money	1,458	198	1,656
Percentage	88.0%	12.0%	100%
Benefits but coping	2,800	401	3,201
Percentage	87.4%	12.6%	100%
Most deprived	1,499	231	1,730
Percentage	86.5%	13.5%	100%
Total	9,602	1,241	10,843
Percentage	88.6%	11.5%	100%
Index of Multiple Deprivation category (measured during pregnancy) χ2 3.9; p: 0.4			
1 (most deprived)	6,416	856	7,272
Percentage	88.2%	11.8%	100%
2	1,748	222	1,970
Percentage	88.7%	11.3%	100%
3	1,076	123	1,199
Percentage	89.7%	10.3%	100%
4	254	32	286
Percentage	88.8%	11.2%	100%
5 (least deprived)	160	15	175
Percentage	91.4%	8.6%	100%
Total	9,654	1,248	10,902
Percentage	88.5%	11.5%	100%
Receipt of Means Tested Benefits (measured during pregnancy) χ2: 13.3; p <0.001			
Yes	3,921	575	4,496
Percentage	87.2%	12.8%	100.0
No	5,702	671	6,373
Percentage	89.5%	10.5%	100.0
Total	9,623	1,246	10,869
Percentage	88.5%	11.5%	100.0
Maternal highest qualification (measured during pregnancy) χ2: 28.0; p <0.001			
<5 GCSE equivalent	2,043	325	2,368
Percentage	86.3%	13.7%	100%
5 GCSE equivalent	2,990	360	3,350
Percentage	89.3%	10.8%	100%
A-level equivalent	1,404	186	1,590
Percentage	88.3%	11.7%	100%
Higher than A-level	2,469	257	2,726
Percentage	90.6%	9.4%	100%
Other or foreign unknown	626	98	724
Percentage	86.5%	13.5%	100%
Total	9,532	1,226	10,758

	no developmental disorder	developmental disorder	total
Percentage	88.6%	11.4%	100%
Child's Ethnicity $\chi 2 = 19.9$; p: 0.001			
White	4,375	626	5,001
Percentage	87.5%	12.5%	100%
Mixed	617	87	704
Percentage	87.6%	12.4%	100%
Asian	6,214	756	6,970
Percentage	89.2%	10.9%	100%
Black	225	20	245
Percentage	91.8%	8.2%	100%
Other	*	*	179
Percentage	*	*	100%
Total	11,602	1,497	13,099
Percentage	88.6%	11.4%	100%
Consanguinity (Mother related to baby's father other than by marriage) $\chi 2 = 7.46$; p: 0.006			
Not related	6,743	825	7,568
Percentage	89.1%	10.9%	100%
Related	2,905	423	3,328
Percentage	87.3%	12.7%	100%
Total	9,648	1,248	10,896
Percentage	88.6%	11.5%	100%
Mother drank alcohol in the first 3 months of pregnancy. $\chi 2$: 1.07; p: 0.3			
No	1,472	177	1,649
Percentage	89.3%	10.7%	100%
Yes	1,432	193	1,625
Percentage	88.1%	11.9%	100%
Total	2,904	370	3,274
Percentage	88.7%	11.3%	100%
Mother drank alcohol since the 4th month of pregnancy. $\chi 2$: 0.09; p: 0.8			
No	1,799	229	2,028
Percentage	88.7%	11.3%	100%
Yes	1,070	141	1,211
Percentage	88.4%	11.6%	100%
Total	2,869	370	3,239
Percentage	88.6%	11.4%	100%
Mother smoked during pregnancy $\chi 2 = 11.69$; p: 0.001			
No	8,103	1,000	9,103
Percentage	89.0%	11.0%	100%
Yes	1,536	246	1,782
Percentage	86.2%	13.8%	100%
Total	9,636	1,246	10,885
Percentage	88.6%	11.5%	100%

Table 74 - Postnatal Characteristics by Developmental Disorder by 12th Birthday (from medical records). Note: missing for >50% of the analysis cohort.

	no developmental disorder	**developmental disorder**	**total**
Breastfeeding - child ever breastfed; χ2: 5.61; p: 0.018			
Yes	2,670	319	2,989
Percentage	89.3%	10.7%	100%
No	759	119	878
Percentage	86.5%	13.6%	100%
Total	3,429	438	3867
Percentage	88.7%	11.3%	100%

Appendix 5.2. Characteristics of the cohort dichotomised by outcome – Special Educational Needs and Disability (SEND) from education records

Table 75 - Neonatal characteristics by Special Educational Needs and Disability (SEND) up to (and including) year 7 (from education records)

	Never any SEND	Ever any SEND	Total
Gestational age χ2 = 46.26; p <0.001			
<34 weeks	100	70	170
Percentage	58.8%	41.2%	100%
34-36 weeks	330	189	519
Percentage	63.6%	36.4%	100
37-38 weeks	1,860	723	2,583
Percentage	72.01	28.0%	100%
39-41 weeks	5,885	2,062	7,947
Percentage	74.1%	26.0%	100%
>41 weeks	107	42	149
Percentage	71.8%	28.2%	100%
Total	8,282	3,086	11,368
Percentage	72.9%	27.2%	100%
Child's Sex χ2: 294.65; p <0.001			
Male	3,861	1,997	5,858
Percentage	65.9%	34.1%	100%
Female	4,421	1,089	5,510
Percentage	80.2%	19.8%	100%
Total	8,282	3,086	11,368
Percentage	72.9%	27.2%	100%
Multiplicity χ2: 0.068; p: 0.8			
Singleton	8,085	3,010	11,095
Percentage	72.9%	27.1%	100%
Twins	197	76	273
Percentage	72.2%	27.8%	100%
Total	8,282	3,086	11,368
Percentage	72.9%	27.2%	100%
Small for gestational age (SGA) χ2: 21.82; p <0.001			
absent	7,006	2,505	9,511
Percentage	73.7%	26.3%	100%
present	1,074	505	1579
Percentage	68.0%	32.0%	100%
Total	8,080	3,010	11,090
Percentage	72.9%	27.1%	100%

Table 76 - Antenatal characteristics by Special Educational Needs and Disability (SEND) from education records up to (and including) year 7

	Never any SEND	**Ever any SEND**	**total**
Maternal age t = 4.51, p <0.0001			
mean	27.7	27.1	27.5
SD	5.6	5.7	5.6
Median	27	27	27
Range	15-45	15-49	15-49
n	8,282	3,086	11,368
Gestational diabetes χ2 = 0.00; p: 0.996			
Absent	7,572	2,815	10,387
Percentage	72.9%	27.1%	100%
Present	662	246	908
Percentage	72.9%	27.1%	100%
Total	8,234	3,061	11,295
Percentage	72.9%	27.1%	100%
Pre-eclampsia χ2 = 3.14; p: 0.077			
Absent	7,713	2,861	10,574
Percentage	72.9%	27.1%	100%
Present	193	90	283
Percentage	68.2%	31.8%	100%
Total	7,906	2,951	10,857
Percentage	72.8%	27.2%	100%

Table 77 – Sociodemographic characteristics by Special Educational Needs and Disability (SEND) up to (and including) year 7 (from education records)

	Never any SEND	**Ever any SEND**	**total**
Socio-economic position: 5 group latent class (measured during pregnancy) χ2: 203.18; p <0.001			
Least deprived, most educated	1,328	308	1,636
Percentage	81.2%	18.8%	100%
Employed not mat deprived	1473	378	1,851
Percentage	79.6%	20.4%	100%
Employed no access to money	1,076	365	1,441
Percentage	74.7%	25.3%	100%
Benefits but coping	1,963	910	2,873
Percentage	68.3%	31.7%	100%
Most deprived	979	567	1,546
Percentage	63.3%	36.7%	100%
Total	6,819	2,528	9,347
Percentage	73.0%	27.1%	100%
Index of Multiple Deprivation group (measured during pregnancy) χ2:45.59; p <0.001			
1 (most deprived)	4,494	1,844	6,338
Percentage	70.9%	29.1%	100%
2	1308	391	1,699
Percentage	77.0%	23.0%	100%
3	773	217	990
Percentage	78.1%	21.9%	100%
4	172	53	225
Percentage	76.4%	23.6%	100%
5 (least deprived)	115	29	144
Percentage	79.9%	20.1%	100%
Total	6,862	2,534	9,396
Percentage	73.0%	27.0%	100%
Receipt of means tested benefits (measured during pregnancy) χ2: 61.92, p <0.001			
Yes	2,781	1,259	4,040
Percentage	68.8%	31.2%	100%
No	4,056	1,272	5,328
Percentage	76.1%	23.9%	100%
Total	6,837	2,531	9,368
Percentage	73.0%	27.0%	100%
Maternal Education (measured during pregnancy) χ2: 150.24, p <0.001			
<5 GCSE equivalent	1,385	750	2,135
Percentage	64.9%	35.1%	100%
5 GCSE equivalent	2,137	850	2,987
Percentage	71.5%	28.5%	100%
A-level equivalent	1,034	325	1,359
Percentage	76.1%	23.9%	100%
Higher than A-level	1,747	417	2,164
Percentage	80.7%	19.3%	100%
other or foreign unknown	473	149	622
Percentage	76.1%	24.0%	100%
Total	6776	2,491	9,267
Percentage	73.1%	26.9%	100%
Child's Ethnicity			

	Never any SEND	Ever any SEND	total
χ2: 22.14; p <0.001			
White	2,957	1,194	4,151
Percentage	71.2%	28.8%	100%
Mixed	469	174	643
Percentage	72.9%	27.1%	100%
Asian	4,595	1655	6,250
Percentage	73.5%	26.5%	100%
Black	125	43	168
Percentage	74.4%	25.6%	100%
Other	132	20	152
Percentage	86.8%	13.2%	100%
Total	8,278	3,086	11,364
Percentage	72.8%	27.2%	100%
Consanguinity (Mother related to baby's father other than by marriage); χ2: 26.69; p <0.001			
absent	4,718	1,601	6,319
Percentage	74.7%	25.3%	100%
present	2,138	933	3,071
Percentage	69.6%	30.4%	100%
Total	6,856	2,534	9,390
Percentage	73.0%	27.0%	100%
Alcohol in first 3 months of pregnancy; χ2: 4.86; p: 0.03			
absent	1041	336.0	1377.0
Percentage	75.6%	24.4%	100%
present	977	382	1,359
Percentage	71.9%	28.1%	100%
Total	2018	718	2,736
Percentage	73.8%	26.2%	100%
Alcohol since 4th month of pregnancy; χ2: 0.05; p: 0.8			
absent	1251	446	1,697
Percentage	73.7%	26.3%	100%
present	740	269	1,009
Percentage	73.3%	26.7%	100%
Total	1991	715	2,706
Percentage	73.6%	26.4%	100%
Smoking during pregnancy; χ2: 35.59; p <0.001			
absent	5,816	2,017	7,833
Percentage	74.3%	25.8%	100%
present	1,034	512	1,546
Percentage	66.9%	33.1%	100%
Total	6,850	2,529	9,379
Percentage	73.0%	27.0%	100%

Table 78 - Postnatal characteristics by Special Educational Needs and Disabilities (SEND) from education records up to (and including) year 7

	Never any SEND	**Ever any SEND**	**total**
Breastfeeding – child ever breastfed; $\chi 2$: 29.92; p <0.001			
Yes Percentage	2,007 76.4%	621 23.6%	2,628 100%
No Percentage	542 66.8%	270 33.3%	812 100%
Total Percentage	2,549 74.1%	891 25.9%	3,440 100%

Note these variables were missing for >50% of the analysis cohort

Appendix 5.3 Confidence intervals for univariable cumulative incidence graphs

Appendix 5.3.1. Developmental disorders from medical records

Table 79 - Cumulative incidence of developmental disorder by gestational age

Gestational age	Cases	total	Cumulative incidence	Logit 95% confidence intervals	
<34 weeks	45	214	21.0%	16.1%	27.0%
34-36 weeks	89	606	14.7%	12.1%	17.7%
37-38 weeks	359	2,950	12.2%	11.0%	13.4%
39-41 weeks	978	9,222	10.6%	10.0%	11.3%
>41 weeks	26	180	14.4%	10.0%	20.4%

Table 80 - Cumulative incidence of developmental disorder by maternal age at child's birth

Maternal age	Cases	total	Cumulative incidence	Logit 95% confidence intervals	
<21 years	165	1,334	12.4%	10.7%	14.2%
21-25	443	3,798	11.7%	10.7%	12.7%
26-30	453	4,201	10.8%	9.9%	11.8%
31-35	261	2,545	10.3%	9.1%	11.5%
>35	175	1,294	13.5%	11.8%	15.5%

Table 81 - Cumulative incidence of developmental disorder by socio-economic position measured by 5 group latent class analysis

	Cases	total	Cumulative incidence	Logit 95% confidence intervals	
Least deprived, most educated	187	2,096	8.9%	7.8%	10.2%
Employed not materially deprived	224	2,160	10.4%	9.2%	11.7%
Employed no access to money	198	1,656	12.0%	10.5%	13.6%
Benefits but coping	401	3,201	12.5%	11.4%	13.7%
Most deprived	231	1,730	13.4%	11.8%	15.0%

Table 82 - Cumulative incidence of developmental disorder by ethnicity

Ethnicity	cases	total	cumulative incidence	Logit 95% confidence intervals	
White	626	5,001	12.5%	11.6%	13.5%
Mixed	87	704	12.4%	10.1%	15.0%
Asian	756	6,970	10.8%	10.1%	11.6%
Black	20	245	8.2%	5.3%	12.3%
Other	*	*	*	*	*

Table 83 - Cumulative incidence of developmental disorder by socioeconomic position for White and Asian children

	cases	total	Cumulative incidence	Logit 95% confidence intervals	
White children					
Least deprived and most educated	61	733	8.3%	6.5%	10.6%
Employed not materially deprived	139	1,414	9.8%	8.4%	11.5%
Employed no access to money	87	667	13.0%	10.7%	15.8%
Benefits but coping	106	675	15.7%	13.1%	18.6%
Most deprived	127	779	16.3%	13.9%	19.1%
Asian children					
Least deprived and most educated	109	1,161	9.4%	7.8%	11.2%
Employed not materially deprived	76	588	12.9%	10.4%	15.9%
Employed no access to money	92	833	11.0%	9.1%	13.4%
Benefits but coping	275	2,362	11.6%	10.4%	13.0%
Most deprived	77	747	10.3%	8.3%	12.7%

Appendix 5.3.2. Special educational needs and disabilities

Table 84 - Cumulative incidence of Special Educational Needs and Disability (SEND) by gestational age

Gestational age	Cases	Total	Cumulative incidence	Logit 95% confidence intervals	
<34 weeks	70	170	41.2%	34.0%	48.7%
34-36 weeks	189	519	36.4%	32.4%	40.6%
37-38 weeks	723	2,583	28.0%	26.3%	29.8%
39-41 weeks	2,062	7,947	25.9%	25.0%	26.9%
>41 weeks	42	149	28.2%	21.6%	35.9%

Table 85 - Cumulative incidence of Special Educational Needs and Disability (SEND) by maternal age at child's birth

Maternal age	Cases of SEND	total	Cumulative incidence	Logit 95% confidence intervals	
<21 years	381	1,160	32.8%	30.2%	35.6%
21-25 years	933	3,312	28.2%	26.7%	29.7%
26-30 years	943	3,596	26.2%	24.8%	27.7%
31-35 years	527	2,175	24.2%	22.5%	26.1%
>35 years	302	1,125	26.8%	24.3%	29.5%

Table 86 - Cumulative incidence of Special Educational Needs and Disability (SEND) by Socio-economic position

Socio-economic position	Cases of SEND	total	cumulative incidence	95% confidence intervals	
Least deprived and most educated	308	1,636	18.8%	17.0%	20.8%
Employed not materially deprived	378	1,851	20.4%	18.6%	22.3%
Employed no access to money	365	1,441	25.3%	23.2%	27.6%
Benefits but coping	910	2,873	31.7%	30.0%	33.4%
Most deprived	567	1,546	36.7%	34.3%	39.1%

Table 87 - Cumulative incidence of Special Educational Needs and Disability (SEND) by ethnicity

Ethnicity	Cases of SEND	total	cumulative incidence	95% confidence intervals	
White	1,194	4,151	28.8%	27.4%	30.2%
Mixed	174	643	27.1%	23.8%	30.6%
Asian	1,655	6,250	26.5%	25.4%	27.6%
Black	43	168	25.6%	19.6%	32.7%
Other	20	152	13.2%	8.6%	19.5%

Table 88 - Cumulative incidence of special educational needs and disabilities (SEND) by socioeconomic position for White and Asian children

	Cases of SEND	total	Cumulative incidence	95% confidence intervals	
White children					
Least deprived and most educated	110	559	19.7%	16.6%	23.2%
Employed not materially deprived	250	1,179	21.2%	19.0%	23.6%
Employed no access to money	152	561	27.1%	23.6%	30.9%
Benefits but coping	214	562	38.1%	34.2%	42.2%
Most deprived	271	663	40.9%	37.2%	44.7%
Asian children					
Least deprived and most educated	174	929	18.7%	16.3%	21.4%
Employed not materially deprived	108	534	20.2%	17.0%	23.8%
Employed no access to money	179	741	24.2%	21.2%	27.4%
Benefits but coping	664	2,169	30.6%	28.7%	32.6%
Most deprived	226	702	32.2%	28.8%	35.7%

Appendix 5.4. Incidence rate of developmental disorders (from medical records) according to covariates of interest

Table 89 - Incidence Rate of Developmental Disorders (from medical records) by neonatal characteristics

	Person-time	Cases	Rate	95% confidence interval	
Gestational age category					
<34 weeks	2321	47	20.25	15.21	26.95
34 – 36 weeks	7389.42	97	13.13	10.76	16.02
37 – 38 weeks	36678.83	385	10.50	9.50	11.60
39 – 41 weeks	116284.2	1084	9.32	8.78	9.89
>41 weeks	2149.75	27	12.56	8.61	18.31
Total	164823.2	1640	9.95	9.48	10.44
Child's sex					
Male	83022.67	1087	13.09	12.34	13.89
Female	81800.5	553	6.76	6.22	7.35
Total	164823.2	1640	9.95	9.48	10.44
Multiplicity					
Singleton	160990.3	1603	9.96	9.48	10.46
Twins	3832.83	37	9.65	6.99	13.32
Total	164823.2	1640	9.95	9.48	10.44
Small for gestational age (SGA)					
not SGA	138678.3	1346	9.71	9.2	10.24
SGA	22244.42	257	11.55	10.22	13.06
Total	160922.7	1603	9.96	9.49	10.46

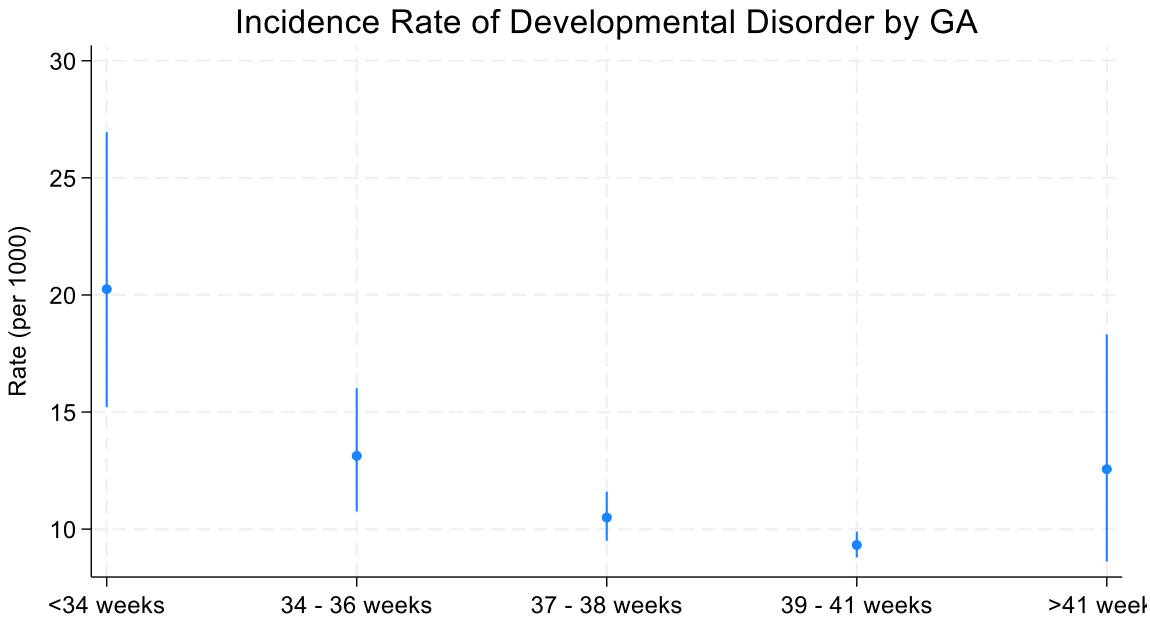


Figure 94 - Incidence rate of developmental disorder by gestational age. Vertical lines indicate 95% confidence intervals

Table 90 - Incidence Rate of Developmental Disorders (from medical records) by antenatal characteristics

	Person-time	**Cases**	**Rate per 1,000 person years**	**95% confidence interval**	
Maternal age category					
<20 years	10282.33	121	11.77	9.85	14.06
20-24 years	42992.83	446	10.37	9.45	11.38
25-29 years	54106.42	508	9.39	8.61	10.24
30-34 years	36814.67	337	9.15	8.23	10.19
35-39 years	17252	183	10.61	9.18	12.26
>40 years	3374.92	45	13.33	9.96	17.86
Total	164823.2	1640	9.95	9.48	10.44
Pre-eclampsia					
absent	153353.3	1522	9.92	9.44	10.44
present	4265	42	9.85	7.28	13.33
Total	157618.3	1564	9.92	9.44	10.43
Gestational diabetes					
absent	150882.8	1488	9.86	9.37	10.38
present	12818.92	139	10.84	9.18	12.8
Total	163701.8	1627	9.94	9.47	10.43

Table 91 - Incidence Rate of Developmental Disorders (from medical records) by socio-demographic characteristics

	Person-time	**Cases**	**Rate per 1,000 person years**	**95% confidence interval**	
Socio-economic position measured by 5 group latent class analysis					
Least deprived and most educated	26493.5	203	7.66	6.68	8.79
Employed not materially deprived	27232.67	246	9.03	7.97	10.24
Employed no access to money	20518.75	214	10.43	9.12	11.92
Benefits but coping	39328.5	433	11.01	10.02	12.1
Most deprived	21365.92	267	12.5	11.08	14.09
Total	134939.3	1363	10.1	9.58	10.65
Index of Multiple Deprivation					
1 (most deprived)	90318.33	928	10.27	9.63	10.96
2	24509.33	255	10.4	9.2	11.76
3	15012.58	139	9.26	7.84	10.93
4	3613.58	34	9.41	6.72	13.17
5 (least deprived)	2257.92	15	6.64	4.01	11.02
Total	135711.8	1371	10.1	9.58	10.65

	Person-time	**Cases**	**Rate per 1,000 person years**	**95% confidence interval**	
Receipt of means tested benefits					
Yes	55241.25	636	11.51	10.65	12.44
No	80018.17	732	9.15	8.51	9.84
Total	135259.4	1368	10.11	9.59	10.66
Maternal highest educational qualification (equivalised)					
<5 GCSEs	29157.33	362	12.42	11.2	13.76
5 GCSE	41950.58	396	9.44	8.55	10.42
A-level	19454.17	206	10.59	9.24	12.14
Higher than A-levels	34376.25	276	8.03	7.14	9.03
other/foreign unknown	9073.42	108	11.9	9.86	14.37
Total	134011.8	1348	10.06	9.54	10.6
Ethnicity					
White	62663.67	729	11.63	10.82	12.51
Mixed	8826.92	97	10.99	9.01	13.41
Asian	86845.67	783	9.02	8.41	9.67
Black	3115	22	7.06	4.65	10.73
Other	2387.58	8	3.35	1.68	6.7
Total	163838.8	1639	10	9.53	10.5
Consanguinity					
absent	94885	937	9.88	9.26	10.53
present	40745.58	434	10.65	9.7	11.7
Total	135630.6	1371	10.11	9.59	10.66
Alcohol in first 3 months of pregnancy					
absent	20982	207	9.87	8.61	11.31
present	20675.58	225	10.88	9.55	12.4
Total	41657.58	432	10.37	9.44	11.4
Alcohol since 4th month of pregnancy					
absent	25785.17	266	10.32	9.15	11.63
present	15360.75	166	10.81	9.28	12.58
Total	41145.92	432	10.5	9.55	11.54
Smoking in pregnancy					
absent	113545.4	1078	9.49	8.94	10.08
present	21951.83	291	13.26	11.82	14.87
Total	135497.3	1369	10.1	9.58	10.65
Ever any breastfeeding					
Yes	37070.83	340	9.17	8.25	10.2
No	10630.58	131	12.32	10.38	14.62
Total	47701.42	471	9.87	9.02	10.81

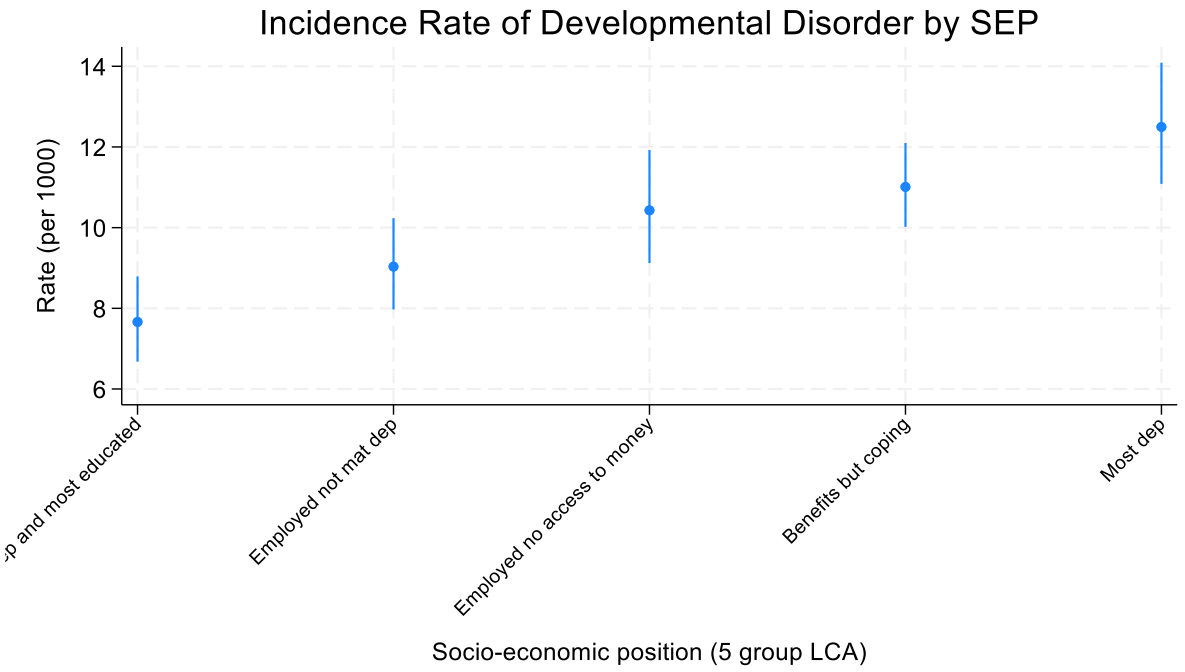


Figure 95 - Incidence rate of developmental disorder by socio-economic position (SEP) measured by 5 groups latent class analysis (LCA). Vertical lines indicate 95% confidence intervals

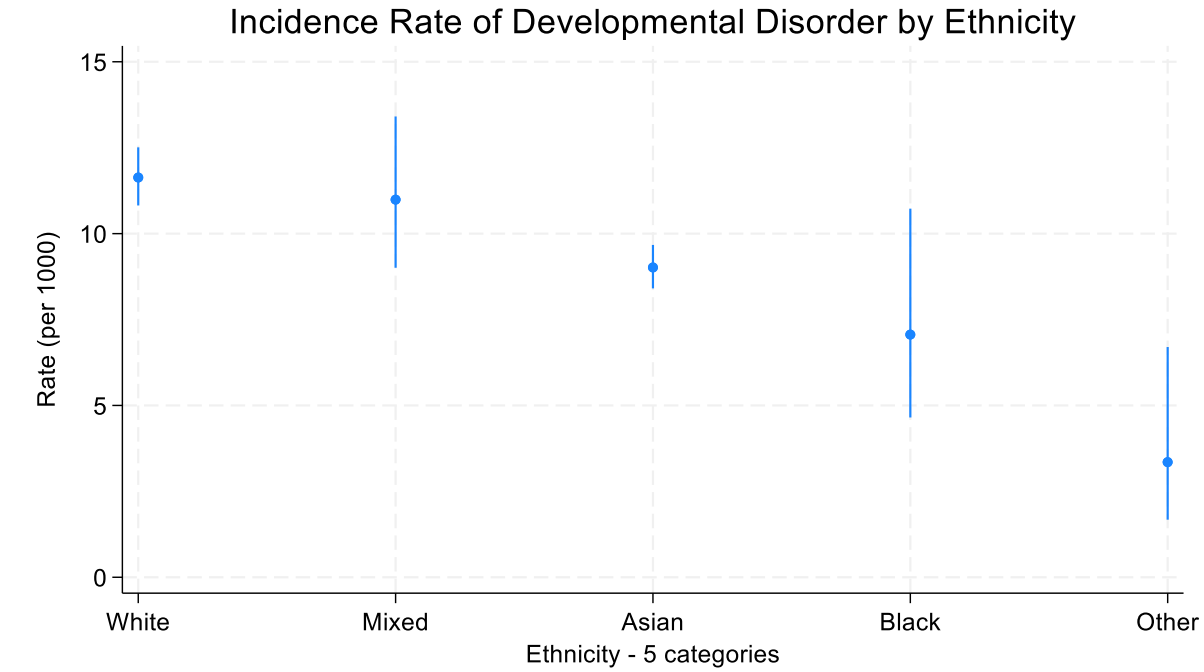


Figure 96 - Incidence rate of developmental disorder by ethnicity. Vertical lines indicate 95% confidence intervals

Appendix 5.5. Incidence rate of Special Educational Need and Disability (SEND) -

Table 92 - Incidence rate of Special Education Need and Disability (SEND) (from education records) by neonatal characteristics

	Person-time	Cases	Rate per 1,000 person years	95% confidence interval	
Gestational age category					
<34 weeks	1904.67	70	36.75	29.08	46.45
34 – 36 weeks	6074.92	197	32.43	28.2	37.29
37 – 38 weeks	31379.25	741	23.61	21.97	25.38
39 – 41 weeks	97648.83	2138	21.89	20.99	22.84
>41 weeks	1770.67	42	23.72	17.53	32.1
Total	138778.3	3188	22.97	22.19	23.78
Child's sex					
Male	68715.58	2049	29.82	28.56	31.14
Female	70062.75	1139	16.26	15.34	17.23
Total	138778.3	3188	22.97	22.19	23.78
Multiplicity					
Singleton	135469.8	3109	22.95	22.16	23.77
Twins	3308.58	79	23.88	19.15	29.77
Total	138778.3	3188	22.97	22.19	23.78
Small for gestational age (SGA)					
not SGA	116684.7	2591	22.21	21.37	23.08
SGA	18717	518	27.68	25.39	30.16
Total	135401.7	3109	22.96	22.17	23.78

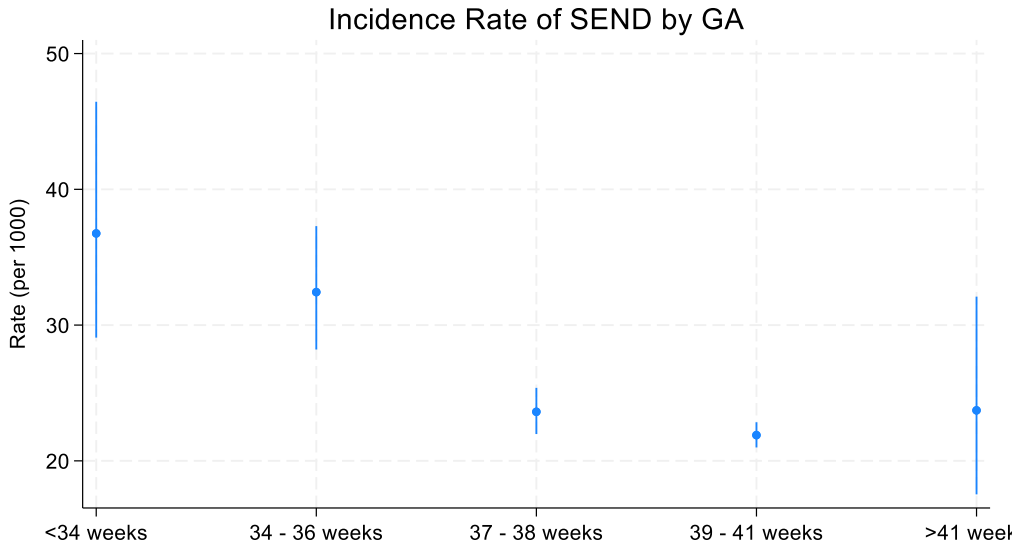


Figure 97 - Incidence rate of Special Education Needs and Disability (SEND) by gestational age. (GA). Vertical lines indicate 95% confidence intervals

Table 93 - Incidence Special Education Need and Disability (SEND) (from education records) antenatal characteristics

	Person-time	**Cases**	**Rate per 1,000 person years**	**95% confidence interval**	
Maternal age category					
<20 years	8538.58	250	29.28	25.87	33.14
20-24 years	36486.33	891	24.42	22.87	26.08
25-29 years	45188.25	1023	22.64	21.29	24.07
30-34 years	31029.25	625	20.14	18.62	21.78
35-39 years	14665.58	324	22.09	19.81	24.63
>40 years	2870.33	75	26.13	20.84	32.77
Total	138778.3	3188	22.97	22.19	23.78
Maternal parity					
0	51237.42	1103	21.53	20.29	22.84
1	39148.92	857	21.89	20.47	23.41
2	23642.75	576	24.36	22.45	26.44
3	11567	318	27.49	24.63	30.69
4	4772	127	26.61	22.37	31.67
5	2037.08	56	27.49	21.16	35.72
>5	6373.17	151	23.69	20.2	27.79
Total	138778.3	3188	22.97	22.19	23.78
Pre-eclampsia					
absent	129249.5	2958	22.89	22.08	23.73
present	3407	91	26.71	21.75	32.8
Total	132656.5	3049	22.98	22.18	23.81
Gestational diabetes					
absent	126875.1	2908	22.92	22.1	23.77
present	11032.67	253	22.93	20.27	25.94
Total	137907.8	3161	22.92	22.14	23.73

Table 94 - Incidence Rate of Special Education Need and Disability (SEND) (from education records) by socio-demographic characteristics

	Person-time	**Cases**	**Rate per 1,000 person years**	**95% confidence interval**	
Socio-economic position measured by 5 group latent class analysis					
Least deprived and most educated	20850.33	318	15.25	13.66	17.02
Employed not materially deprived	23311.25	392	16.82	15.23	18.57
Employed no access to money	17697.25	376	21.25	19.2	23.51
Benefits but coping	34134.17	942	27.6	25.89	29.42
Most deprived	17907.83	584	32.61	30.07	35.37
Total	113900.8	2612	22.93	22.07	23.83
Index of Multiple deprivation					
1 (most deprived)	76297	1897	24.86	23.77	26.01
2	21212.83	406	19.14	17.37	21.09
3	12435.33	230	18.5	16.25	21.05
4	2819	57	20.22	15.6	26.21
5 (least deprived)	1818.92	30	16.49	11.53	23.59
Total	114583.1	2620	22.87	22.01	23.76
Receipt of means tested benefits					
Yes	47963.67	1302	27.15	25.71	28.66
No	66239	1314	19.84	18.79	20.94
Total	114202.7	2616	22.91	22.05	23.8
Maternal highest educational qualification					
<5 GCSEs	25010.67	772	30.87	28.76	33.12
5 GCSE	36280.92	880	24.26	22.7	25.91
A-level	16591.5	332	20.01	17.97	22.28
Higher than A-levels	27501.5	430	15.64	14.23	17.19
other or foreign unknown	7710.17	162	21.01	18.01	24.51
Total	113094.8	2576	22.78	21.91	23.67
Ethnicity					
White	50636.58	1246	24.61	23.28	26.01
Mixed	7817.5	182	23.28	20.13	26.92
Asian	76129	1696	22.28	21.24	23.36
Black	2079.92	43	20.67	15.33	27.88
Other	2032.58	21	10.33	6.74	15.85
Total	138695.6	3188	22.99	22.2	23.8
Consanguinity					
absent	77948	1667	21.39	20.38	22.44
present	36550	953	26.07	24.47	27.78
Total	114498	2620	22.88	22.02	23.78
Alcohol in first 3m of pregnancy					
absent	17152.5	357	20.81	18.76	23.09

	Person-time	**Cases**	**Rate per 1,000 person years**	**95% confidence interval**	
present	16660.33	398	23.89	21.65	26.36
Total	33812.83	755	22.33	20.79	23.98
Alcohol since 4th month of pregnancy					
absent	20917.83	474	22.66	20.71	24.79
present	12484.75	278	22.27	19.8	25.04
Total	33402.58	752	22.51	20.96	24.18
Smoking in pregnancy					
absent	96001.75	2080	21.67	20.75	22.62
present	18386.58	535	29.1	26.73	31.67
Total	114388.3	2615	22.86	22	23.75
Ever breastfed					
Yes	32338.08	638	19.73	18.26	21.32
No	9476.5	280	29.55	26.28	33.22
Total	41814.58	918	21.95	20.58	23.42

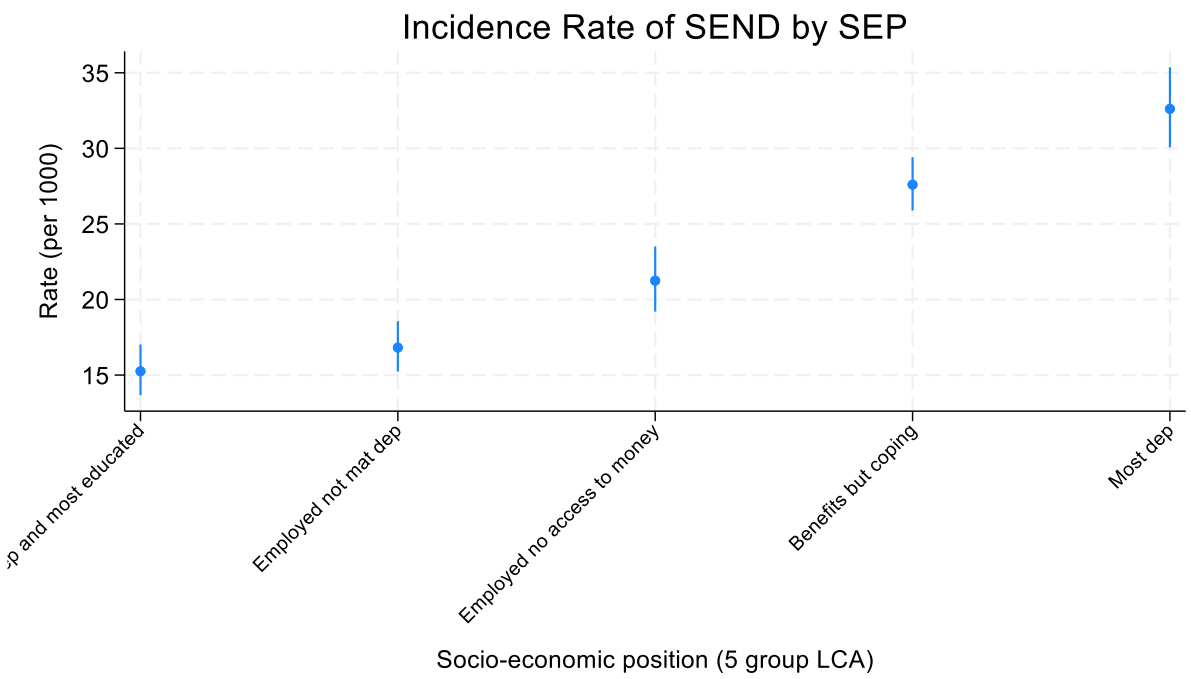


Figure 98 - Incidence rate of Special Education Needs and Disability (SEND) by socio-economic position (SEP) measured by 5 groups latent class analysis (LCA).

Vertical lines indicate 95% confidence intervals

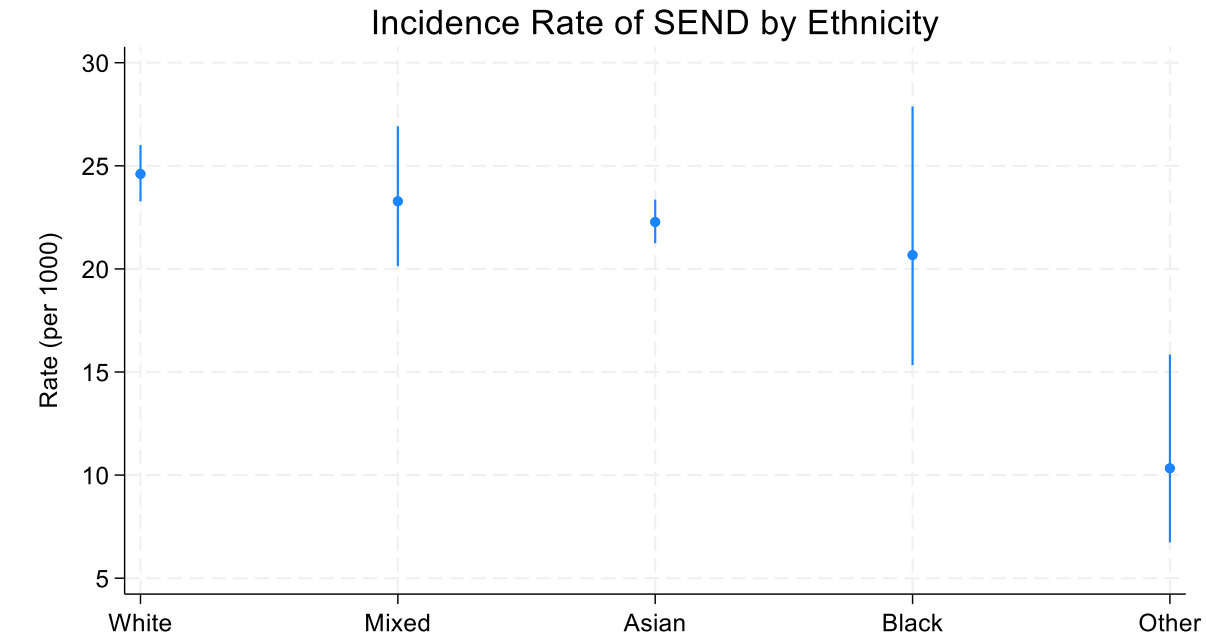


Figure 99 - Incidence rate of Special Education Needs and Disability (SEND) by ethnicity.

Appendix 5.6. Incidence rate of individual developmental disorders by gestational age

Table 95 - Incidence rate of each developmental disorder, according to gestational age category

*Person time per 1,000 children, rate per 1,000 person years. * Suppressed if one cell <10 cases to avoid possible deductive disclosure*

	<34 weeks, N = 214	**34 - 36 weeks, N = 606**	**37 - 38 weeks, N = 2,950**	**39 - 41 weeks, N = 9,222**	**>41 weeks, N = 180**
Cerebral palsy					
cases	14	*	*	25	*
Person time	2.64			124.76	
Rate	5.31 (3.14 - 8.96)			0.20 (0.14- 0.30)	
Motor function problems					
cases	*	*	23	55	*
Person time			39.64	124.49	
Rate			0.58 (0.39 - 0.87)	0.44 (0.34 - 0.58)	
Learning disability (intellectual disability)					
cases	*	15	49	137	*
Person time		8.12	39.59	124.29	
Rate		1.85 (1.11 - 3.06)	1.24 (0.94 -1.64)	1.10 (0.93 - 1.30)	
Education problems					
cases	*	21	88	211	*
Person time		8.05	39.28.	123.7	
Rate		2.61 (1.70-4.00)	2.24 (1.82 – 2.76)	1.71 (1.49-1.95)	
Speech, language, and communication disorders					
cases	*	38	139	404	*
Person time		7.81	38.49	121.13	
Rate		4.87 (3.54-6.69)	3.61 (3.06-4.26)	3.34 (3.03-3.68)	
Attention deficit hyperactivity disorder (ADHD)					
cases	*	*	41	105	*
Person time			39.70	124.66	
Rate			1.03 (0.76 -1.40)	0.84 (0.70 -1.02)	
Autism spectrum disorder (ASD)					
cases	*	16	91	260	*

	<34 weeks, N = 214	**34 - 36 weeks, N = 606**	**37 - 38 weeks, N = 2,950**	**39 - 41 weeks, N = 9,222**	**>41 weeks, N = 180**
Person time		8.10	39.44	123.79	
Rate		1.97 (1.21-3.22)	2.31 (1.88-2.83)	2.10 (1.86-2.37)	
Social, emotional, and behavioural problems					
cases	*	20	76	254	*
Person time		8.12	39.46	123.77	
Rate		2.46 (1.59-3.82)	1.93 (1.54-2.41)	2.05 (1.81-2.32)	
Feeding problems					
cases	*	*	10	39	*
Person time			39.74	124.59	
Rate			0.25 (0.14 - 0.47)	0.31 (0.23 - 0.43)	
Sleep apnoea					
cases	*	16	51	144	*
Person time		8.04	39.47	123.88	
Rate		1.99 (1.22-3.25)	1.29 (0.98-1.70)	1.16 (0.99-1.37)	
Visual impairment					
cases	*	*	21	54	*
Person time			39.67	124.54	
Rate			0.53 (0.35-0.81)	0.43 (0.33-0.57)	
Hearing impairment					
cases	*	*	15	54	*
Person time			39.71	124.47	
Rate			0.38 (0.23-0.63)	0.43 (0.33-0.57)	
Developmental delay					
cases	17	23	64	168	*
Person time	2.61	7.96	39.2	123.30	
Rate	6.52 (4.05-10.49)	2.89 (1.92-4.35)	1.63 (1.28-2.08)	1.36 (1.17-1.58)	
Unspecified developmental disorder					
cases	*	*	21	55	*
Person time			39.68	124.49	
Rate			0.53 (0.35-0.81)	0.44 (0.34-0.58)	

Appendix 5.7. Options for modelling gestational age and developmental disorder

Continuous linear model

Table 96 - Odds ratio of developmental disorder from logistic regression where gestational age is treated as a continuous variable

	Odds ratio	**95% conf. interval**		**p value**
Gestational age in weeks	0.93	0.90	0.95	<0.001

Number of observations = 13,172

This model shows that with every increasing week of gestation the odds of a developmental disorder decrease by 0.07, i.e. 7%. However, in reality when children are post-term, the risk increases, and this is reflected in the data, for example, see Figure 76. A possible solution would have been to drop all the children born post term (180 participants born >41 weeks), but this would result in loss of data.

Continuous with a quadratic term

Table 97 - Odds ratio of developmental disorder from logistic regression where gestational age is treated as a continuous variable with a quadratic term

	Odds ratio	**95% conf. interval**		**p value**
gestation	0.62	0.42	0.91	0.02
c.gestation#c.gestation	1.01	1.00	1.01	0.04

Number of observations = 13,172

This shows that there was a statistically significant relationship between *gestational age in weeks* and *gestational age in weeks*^{2} and the outcome variable developmental disorder. The addition of the quadratic term led to a small reduction in Akaike's information criterion (from 9,322.4 without the quadratic term to 9,320.0 with it) and a small increase in the Bayesian information criterion (from 9337.4 without the quadratic term to 9342.5 with the quadratic term). Given this and the added complexity it brings to the model the quadratic approach was not pursued further.

Categories for each week of gestation compared to a 40-week reference category

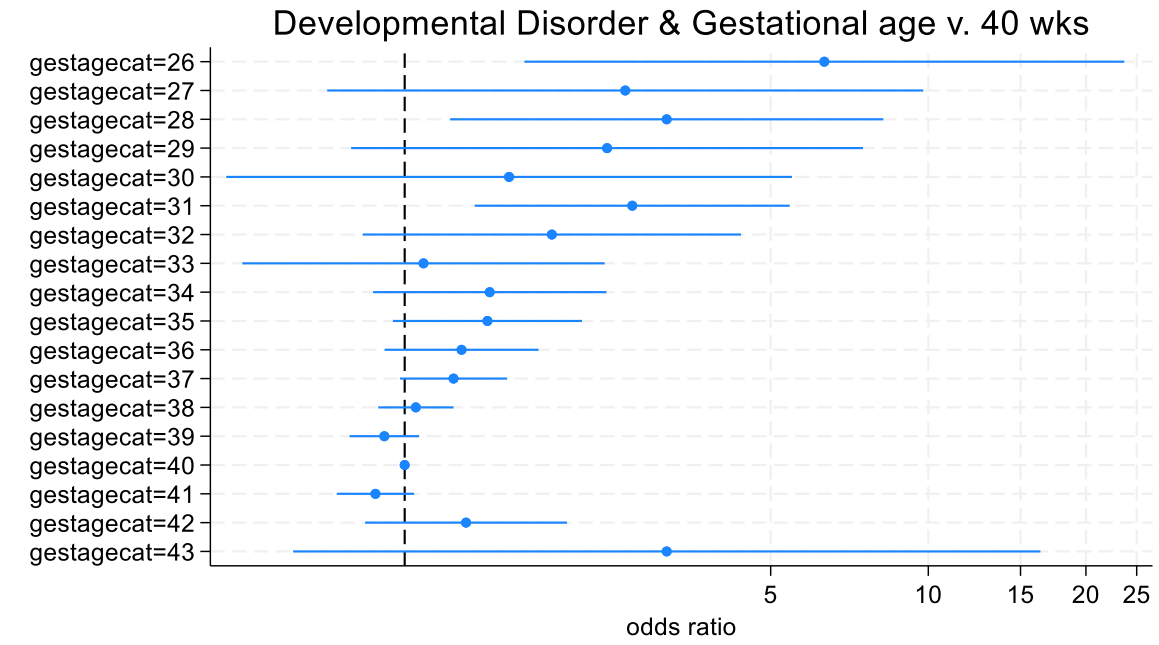
Gestational age was treated as a categorical variable. This allowed for the increase in cumulative incidence of developmental disorders which is observed post term.

The children born <26 weeks were combined into one group. Treating each week of gestational age as a separate category resulted in small groups and non-significant p values in all the groups (except for ≤26 weeks, 28 weeks and 31 weeks gestation). This approach also meant some observations had to be dropped as there were no events in that category.

Table 98 - Odds ratio of developmental disorder from logistic regression, each week of gestation is a separate category, compared to 40 weeks

Gestational age, weeks	Odds ratio	95% conf. interval		P value
≤26	6.33	1.69	23.67	0.006
27	2.64	0.71	9.78	0.1
28	3.17	1.22	8.2	0.02
29	2.44	0.79	7.5	0.1
30	1.58	0.46	5.49	0.5
31	2.72	1.36	5.44	0.005
32	1.91	0.83	4.39	0.1
33	1.09	0.49	2.41	0.8
34	1.45	0.87	2.43	0.1
35	1.44	0.95	2.18	0.09
36	1.28	0.92	1.8	0.1
37	1.24	0.98	1.57	0.07
38	1.05	0.89	1.24	0.6
39	0.91	0.78	1.07	0.3
40	1.00 (reference)			
41	0.88	0.75	1.04	0.1
42	1.31	0.84	2.04	0.2
43	3.17	0.61	16.4	0.2
44	omitted			

Number of observations = 13,168



Note. Data source: BiB - analysis cohort - up to age 12

Figure 100 - Odds ratio (with 95% confidence intervals) of developmental disorder from logistic regression, each week of gestation is a separate category, compared to 40 weeks

Appendix 5.8. Modelling incidence rate of developmental disorder

A test for overdispersion was carried out using the *overdisp* command. The t test of the coefficient of û indicates the non-equi dispersion (i.e. overdispersion) (p <0.001), thus favouring negative binomial regression, as opposed to Poisson regression (Fávero et al., 2020).

Table 99 - Incidence rate ratios of developmental disorder from Poisson regression, with gestational age categories, compared to full term reference category

	Incidence rate ratio	95% confidence interval		P-value
<34 weeks	2.17	1.62	2.91	<0.001
34-36 weeks	1.41	1.14	1.73	0.001
37-38 weeks	1.13	1.00	1.26	0.05
39-41 weeks	1.00 (reference)			
>41 weeks	1.35	0.92	1.97	0.1

Number of observations 13,172

The results of the negative binomial regression are shown below.

Table 100 - Incidence rate ratios of developmental disorder from negative binomial regression, with gestational age categories, compared to full term reference category

	Incidence rate ratio	**95% confidence interval**		**P value**
<34 weeks	3.92	2.35	6.52	<0.001
34 - 36 weeks	1.64	1.20	2.24	0.002
37 - 38 weeks	1.19	1.01	1.41	0.04
39-41 weeks	1.00 (reference)			
>41 weeks	1.43	0.81	2.50	0.2

Number of observations = 13,144

Appendix 5.9. Modelling cumulative incidence of developmental disorder and gestational age – complete case analysis

Table 101 - Results of logistic regression model for association of gestational age with developmental disorder. Overall/global p-values shown for variables with multiple categories. Complete case analysis.

	Odds ratio	95% confidence interval		P value
Gestational age				
<34 weeks	2.50	1.67	3.75	<0.001
34 - 36 weeks	1.37	1.02	1.82	0.03
37 - 38 weeks	1.18	1.02	1.37	0.03
39-41 weeks	1.00 (reference)			
>41 weeks	1.66	1.07	2.56	0.02
Child's sex				
Male	2.16	1.90	2.46	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.25	1.06	1.49	0.01
Maternal age (in years) at child's delivery				
<21	0.95	0.74	1.22	0.7
21-25	1.14	0.95	1.37	0.2
26-30	1.03	0.86	1.24	0.8
31-35	1.00 (reference)			
>35	1.38	1.10	1.74	0.006
Socio-economic position - Five group latent class analysis				
Least deprived	1.00 (reference)			
Employed not mat deprived	1.11	0.90	1.38	0.3
Employed no access to money	1.41	1.13	1.76	0.002
Benefits but coping	1.51	1.24	1.84	<0.001
Most deprived	1.56	1.25	1.94	<0.001
Ethnicity				
White	1.17	1.00	1.36	0.05
Mixed	1.01	0.75	1.35	1.0
Asian	1.00 (reference)			
Black	0.95	0.58	1.55	0.8
Other	0.55	0.25	1.20	0.1
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.13	0.95	1.36	0.2

Number of observations: 10,553

Appendix 5.10. Model Diagnostics: developmental disorder from medical records (complete case analysis)

Goodness of fit

Goodness-of-fit tests are not directly applicable to multiple imputation results (StataCorp, nd.). Therefore, the model diagnostics were carried out on the complete case analysis. Hosmer-Lemeshow goodness-of-fit test showed a $\chi 2 = 4.33$, p-value = 0.8, indicating a good fit.

Model discrimination

A graph showing sensitivity and specificity of the model was produced, as shown below. This shows that the optimal probability cut off is 0.12. Using a cut-off of 0.12 the *estat classification* command was used, which shows the model would correctly classify 59.6% of children.

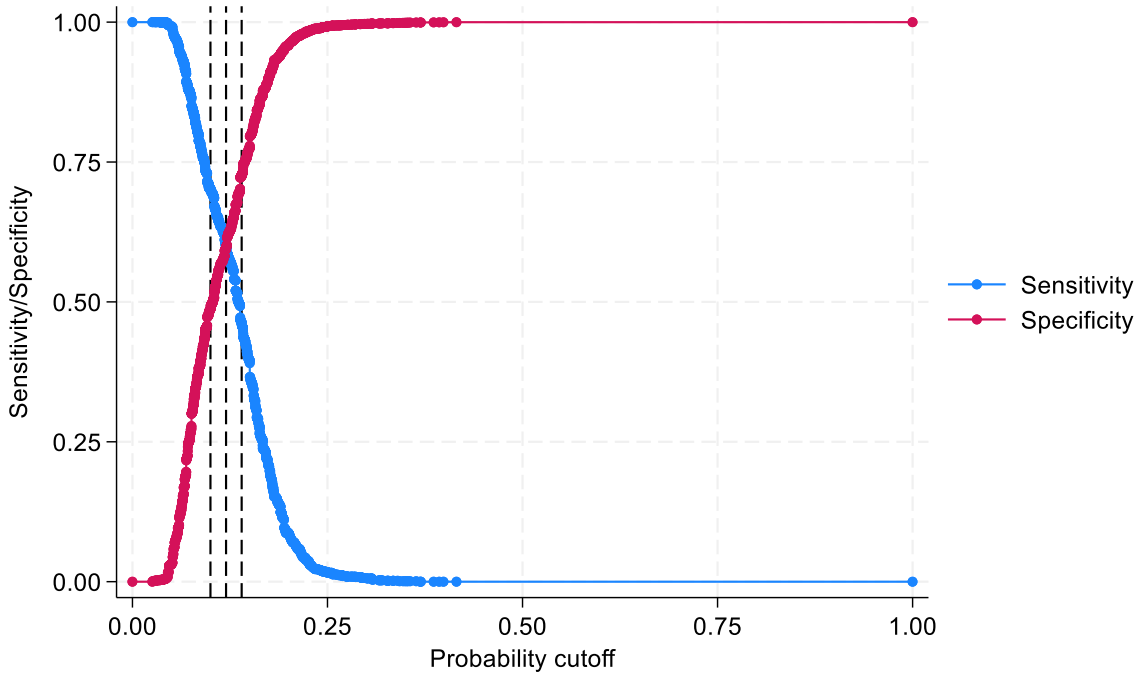


Figure 101 - Sensitivity and specificity of developmental disorder and gestational age model versus probability cut off.

Dotted lines indicating probabilities of 0.10, 0.12, 0.14

A receiver operating characteristic curve (ROC curve) was plotted. This showed an area under the curve (AUC) of 0.64, see figure below; an AUC of 1 indicates a perfect test and an AUC of 0.5 is no better than random (Hand, 2010).

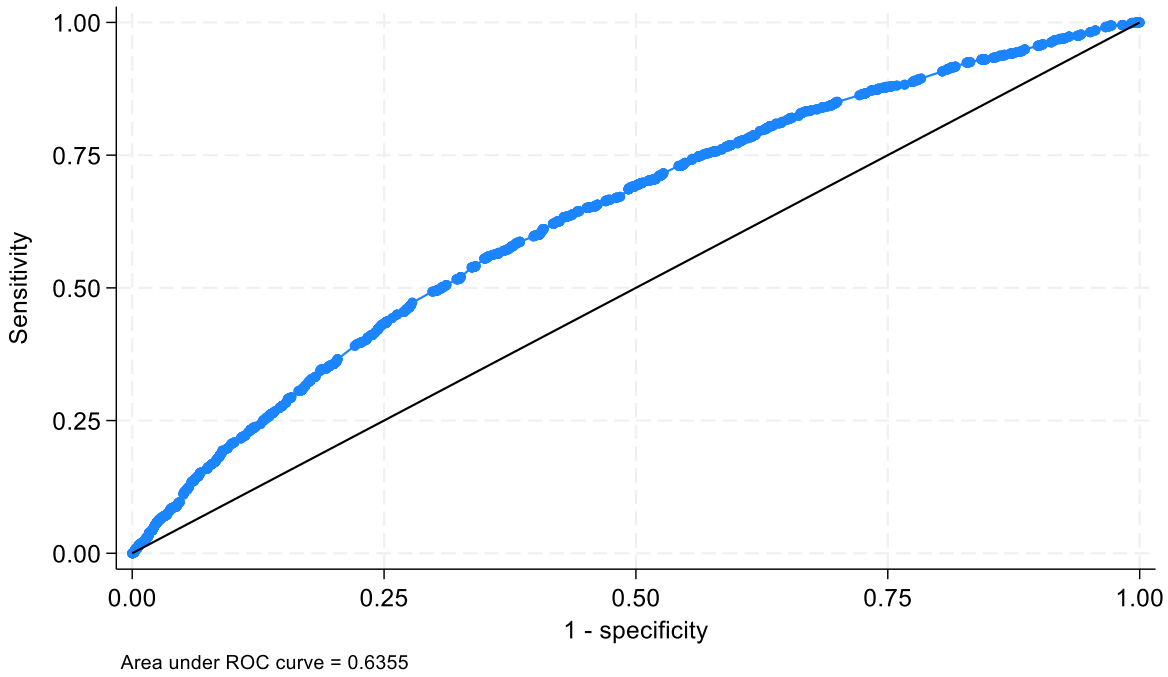


Figure 102 - Receiver operating characteristic (ROC) curve for developmental disorder and gestational age model

Influential Covariate patterns

Pregibon's delta beta influence statistic was plotted. The change in Pearson chi-square statistic when an observation is removed was plotted. There were no covariate patterns which appeared to be potentially influential on all three tests.

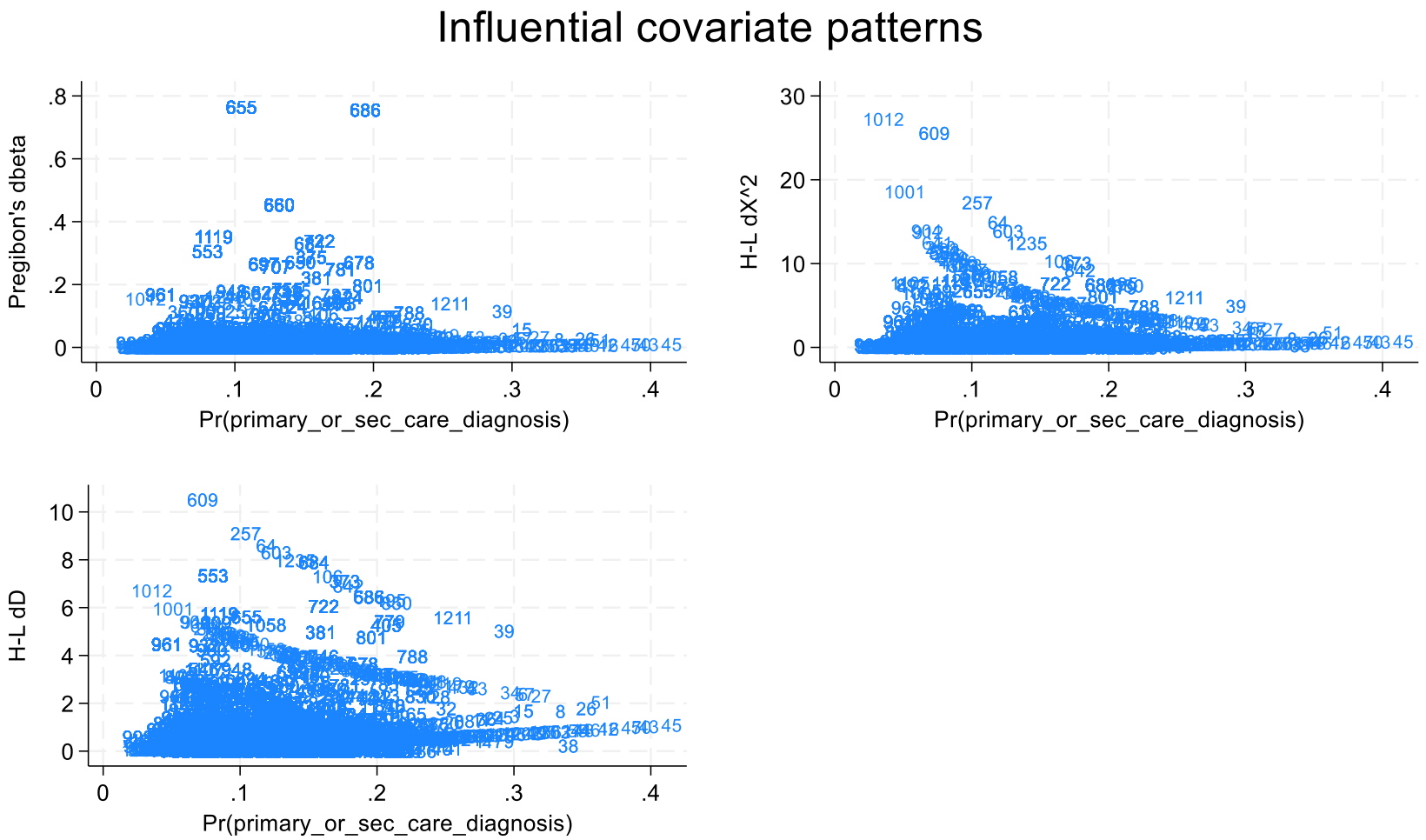


Figure 103 - Pregibon dbeta, Change in Person chi-sq statistics, Change in deviance (difference of log likelihood) plotted against probability of developmental disorder

Influential Outliers

Pearson's Residuals, Standardised Pearson's Residuals and Deviance Residuals were plotted, see Figure 104 below. This showed covariate pattern 51 could be an outlier as it slightly removed from the bulk of the other points in all three graphs. The regression was repeated excluding this covariate pattern (Table 102). Exclusion of this covariate pattern reduced the odds ratio for the <34 week group slightly. All other results remained essentially unchanged.

Table 102 - Results of logistic regression model, association of gestational age with developmental disorders, excluding covariate pattern 51.

	Odds ratio	**95% confidence interval**		**P value**
Gestational age				
<34 weeks	2.44	1.62	3.66	<0.001
34 - 36 weeks	1.37	1.02	1.82	0.03
37 - 38 weeks	1.18	1.02	1.37	0.03
39-41 weeks	1.00 (reference)			
>41 weeks	1.66	1.07	2.56	0.02
Child's sex				
Male	2.16	1.90	2.46	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.25	1.05	1.48	0.01
Maternal age (in years) at child's delivery				
<21	0.95	0.74	1.22	0.7
21-25	1.14	0.95	1.37	0.2
26-30	1.03	0.86	1.24	0.8
31-35	1.00 (reference)			
>35	1.38	1.10	1.74	0.006
Socio-economic position - Five group latent class analysis				
Least deprived	1.00 (reference)			
Employed not mat deprived	1.11	0.90	1.38	0.3
Employed no access to money	1.41	1.13	1.76	0.002
Benefits but coping	1.51	1.24	1.84	<0.001
Most deprived	1.55	1.24	1.93	<0.001
Ethnicity				
White	1.17	1.00	1.36	0.05
Mixed	1.01	0.75	1.35	1.0
Asian	1.00 (reference)			
Black	0.95	0.58	1.55	0.8
Other	0.55	0.25	1.20	0.1
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.13	0.95	1.36	0.2

N = 10,552

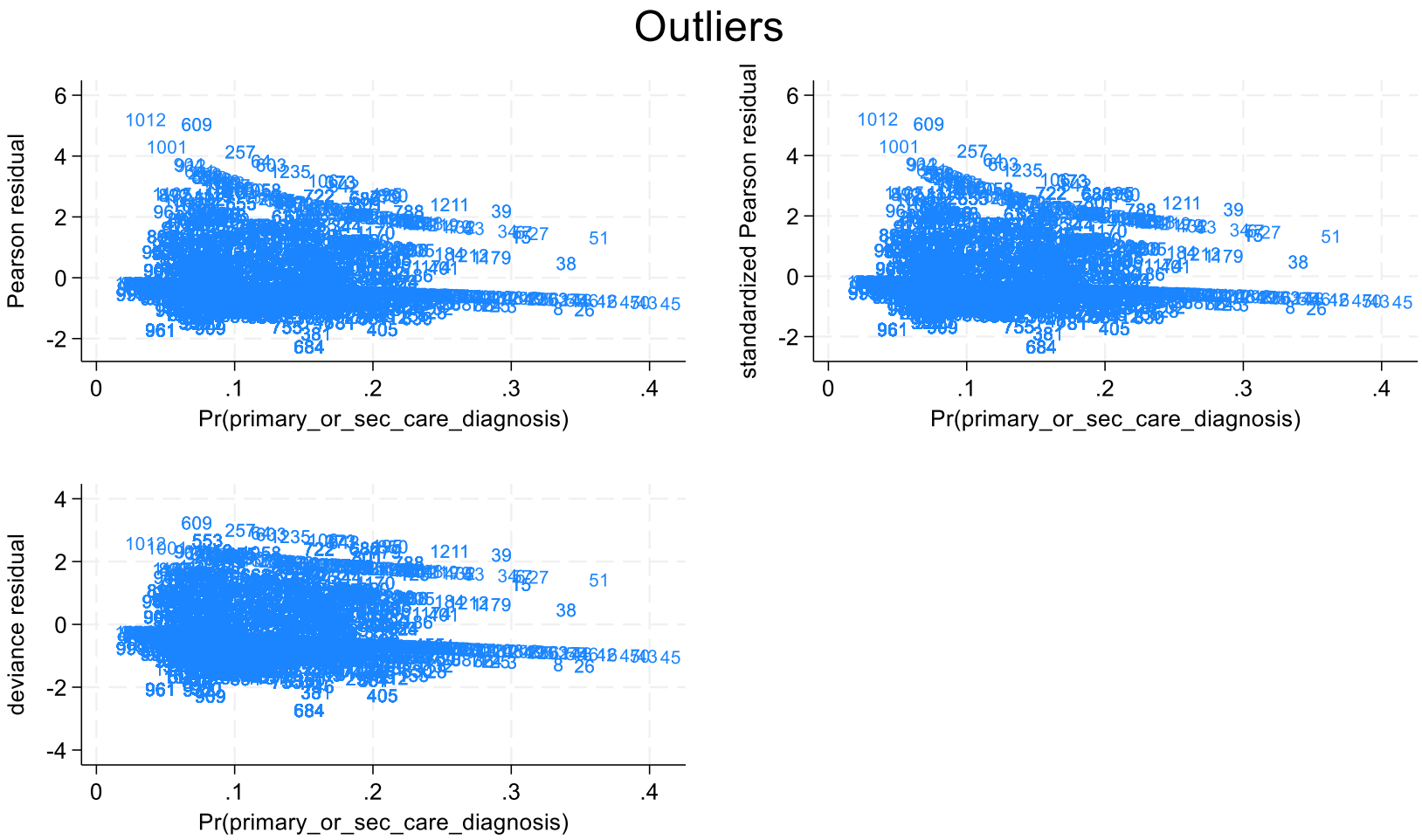


Figure 104 - Pearson's Residuals, Standardised Pearson's Residuals and Deviance Residuals plotted against probability of developmental disorder

Appendix 5.11. Alternative measure of socio-economic position, developmental disorder

Table 103 – Adjusted logistic regression model, odds ratio of developmental disorder by gestational age.

	Odds ratio	**95% confidence interval**		**P value**
Gestational age				
<34 weeks	2.55	1.70	3.82	<0.001
34 - 36 weeks	1.41	1.06	1.88	0.02
37 - 38 weeks	1.22	1.06	1.42	0.008
39-41 weeks	1.00 (reference)			
>41 weeks	1.67	1.08	2.58	0.02
Child's sex				
Male	2.17	1.91	2.47	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.29	1.08	1.53	0.004
Maternal age (in years) at child's delivery				
<21	1.02	0.79	1.31	0.9
21-25	1.17	0.97	1.41	0.1
26-30	1.03	0.86	1.24	0.7
31-35	1.00 (reference)			
>35	1.34	1.07	1.70	0.01
Mother's highest educational qualification				
<5 GCSE equivalent	1.38	1.14	1.67	0.001
5 GCSE equivalent	1.07	0.89	1.28	0.5
A-level equivalent	1.22	0.99	1.50	0.07
Higher than A-level	1.00 (reference)			
other or foreign unknown	1.39	1.07	1.81	0.01
Receipt of means tested benefits (MTB)				
No MTB	1.00 (reference)			
MTB	1.20	1.05	1.36	0.007
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.13	0.95	1.36	0.2
Ethnicity				
White	1.11	0.96	1.28	0.2
Mixed	0.93	0.70	1.25	0.6
Asian	1.00 (reference)			
Black	0.98	0.60	1.59	0.9
Other	0.51	0.24	1.10	0.09

Number of observations: 10,433

Appendix 5.12. Imputation: developmental disorder and gestational age

There were nine patterns of missingness. The majority of these were seen in less than 1% of the analysis cohort. The patterns of missingness are shown below in Table 104. Child's sex and maternal age are not shown as they were complete.

Table 104 - Patterns of missingness.

Percent. of cohort	Ethnicity	Small for gestational age	smoking	5 group latent class analysis
80%	1	1	1	1
16%	1	1	0	0
2%	1	0	1	1
<1%	0	1	0	0
<1%	1	1	1	0
<1%	1	0	0	0
<1%	1	1	0	1
<1%	0	1	1	0
<1%	0	0	0	0
<1%	1	0	1	0

0 = missing, 1 = non-missing.

Selection of auxiliary variables

The following auxiliary variables were considered:

1. Pre-eclampsia
2. Gestational diabetes (GDM)
3. Consanguinity
4. IMD categories
5. Parity

A binary variable identifying missingness for each variable of interest with missing data was created. These identifier variables were regressed (using logistic regression) on the potential auxiliary variables to determine whether they were associated with missingness in the variables of interest.

Table 105 - Regression of missing SGA flag variable against potential auxiliary variables:

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.33	0.21	0.52	<0.001
GDM	0.52	0.37	0.72	<0.001
Consanguinity	0.87	0.67	1.12	0.3
IMD category	0.90	0.80	1.02	0.09
Parity	1.00	0.90	1.07	0.7

Table 106 - Regression of missing 5 group latent class analysis flag variable against potential auxiliary variables

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.92	0.70	1.21	0.6
GDM	1.26	1.05	1.5	0.01
Consanguinity	1.80	0.96	3.39	0.07
IMD category	1.30	0.92	1.82	0.1
Parity	0.87	0.84	0.90	<0.001

Table 107 - Regression of missing ethnicity flag variable against potential auxiliary variables:

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.42	0.15	1.17	0.1
GDM	1.10	0.44	2.74	0.8
Consanguinity	1	Non-missing consanguinity predicts success perfectly		
IMD categories	1.39	0.27	7.15	0.7
Parity	1.02	0.84	1.22	0.9

Table 108 - Regression of missing smoking flag variable against potential auxiliary variables:

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.90	0.68	1.19	0.5
GDM	1.27	1.06	1.52	0.01
Consanguinity	0.60	0.24	1.50	0.3
IMD quintiles	0.94	0.59	1.48	0.8
Parity	0.86	0.83	0.89	<0.001

Pre-eclampsia, gestational diabetes, consanguinity, and maternal parity were associated with the odds of missingness in at least one of the analyses. Therefore, they were included in the imputation as auxiliary variable. Twenty five imputations were carried out as this exceeds the overall percentage of missing data (White et al., 2011). The imputations were carried out according to the type of variable, as follows:

- Logistic regression:
    - Gestational diabetes
    - Pre-eclampsia
    - Small for gestational age
    - Consanguinity
    - Smoking
- Multinomial logistic regression
    - Ethnicity
- Ordered logistic regression
    - 5 group latent class analysis
    - Parity

Appendices

Imputation diagnostics

The distributions of the imputed, observed, and overall values were compared using the *midiagplots* command (Eddings, 2012). This shows that the proportion in each category in the final (completed) dataset, containing imputed and observed values, is very similar to the observed values, although there is some variation is the imputed data.

Table 109 - Imputed, observed, and final (completed) values. Total n 13,172. 25 imputations

	Observed	**Imputed**	**Completed**
Ethnicity			
White	38.2%	38.4%	38.2%
Mixed	5.4%	2.7%	5.4%
Asian	53.2%	56.2%	53.2%
Black	1.9%	1.4%	1.9%
Other	1.4%	1.4%	1.4%
Small for Gestational Age (SGA)			
not SGA	86.0%	92.3%	86.2%
SGA	14.0%	7.7%	13.8%
Smoking in pregnancy			
no smoking	83.6%	83.6%	83.6%
smoking	16.4%	16.4%	16.4%
Socio-economic position – 5 group latent class analysis			
Least deprived and most educated	19.3%	17.0%	18.9%
Employed not materially deprived	19.9%	21.3%	20.2%
Employed no access to money	15.3%	14.6%	15.1%
Benefits but coping	29.5%	30.1%	29.6%
Most deprived	16.0%	17.0%	16.1%

Appendix 5.13. Modelling Gestational age and Special Educational Needs and Disability

As with developmental disorders from medical records, four different options for modelling the relationship between gestational age and Special Educational Needs and Disability (SEND) were explored:

Continuous linear model

This model shows that with every additional week of gestation the odds of SEND decrease by 0.07. However, when children are post-term, the cumulative incidence of SEND increases (Figure 81), therefore this model does not represent the data well. A possible solution would have been to drop all the children born post term, but this would result in loss of data.

Table 110 - Odds ratio of Special Educational Needs and Disability (SEND) from logistic regression where gestational age is treated as a continuous variable

	Odds ratio	**95% confidence interval**		**P value**
gestation (to last complete week)	0.93	0.91	0.95	<0.001

Number of observations = 11,368

Continuous with quadratic term added

The quadratic term is not statistically significant; therefore, this approach will not be used.

Table 111 - Odds ratio of Special Educational Needs and Disability (SEND) from logistic regression where gestational age is treated as a continuous variable with a quadratic term

	Odds ratio	**95% conf. interval**		**p value**
gestation	0.71	0.49	1.01	0.06
c.gestation#c.gestation	1.00	1.00	1.01	0.1

Number of observations = 11,368

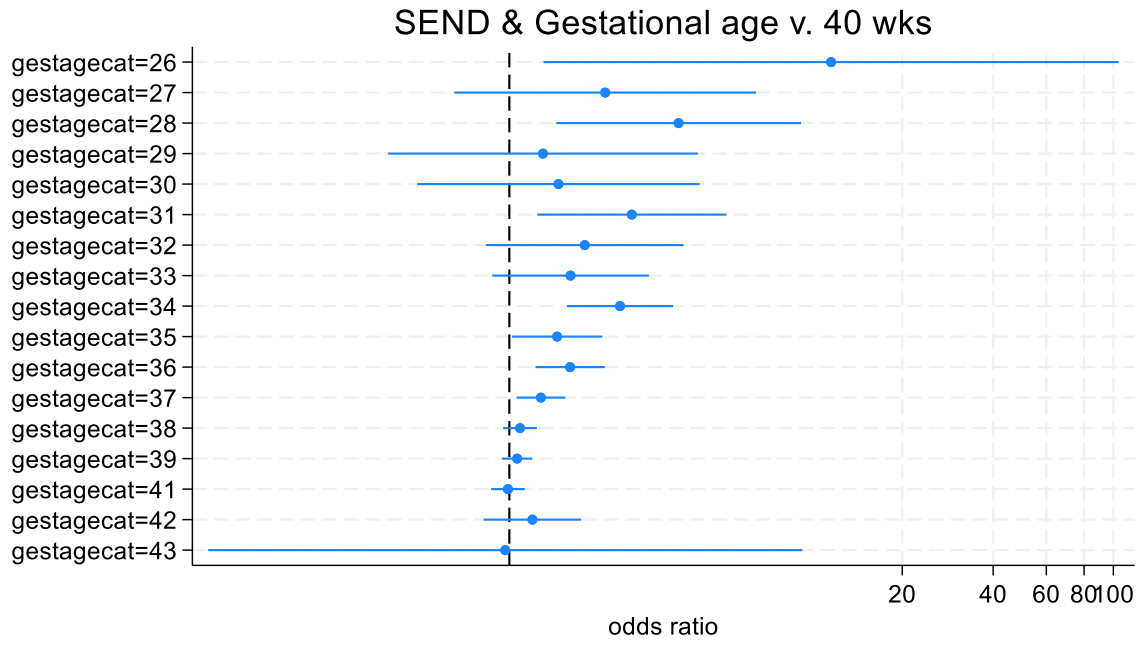
Categories for each week of gestation compared to a 40-week reference category

Gestational age was treated as a categorical variable. This allowed for the increase in cumulative incidence of SEND demonstrated in the post term children, shown in Figure 81. The children born <26 weeks were combined into one group. This approach results in small groups and non-significant p values in several groups, as shown in Table 112. This approach also meant some observations had to be dropped as there were no events in that category.

Table 112 - Odds ratio of SEND from logistic regression, each week of gestation is a separate category, compared to 40 weeks

Gestational age, weeks	Odds ratio	95% confidence interval		P value
≤26	11.63	1.3	104.15	0.03
27	2.08	0.66	6.56	0.2
28	3.63	1.43	9.24	0.007
29	1.29	0.4	4.21	0.7
30	1.45	0.5	4.27	0.5
31	2.54	1.24	5.24	0.01
32	1.78	0.84	3.78	0.1
33	1.59	0.88	2.9	0.1
34	2.33	1.55	3.49	<0.001
35	1.44	1.02	2.03	0.04
36	1.59	1.22	2.07	0.001
37	1.27	1.06	1.53	0.01
38	1.09	0.95	1.23	0.2
39	1.06	0.94	1.19	0.3
40	1.00 (Reference)			
41	0.99	0.87	1.13	0.9
42	1.19	0.82	1.73	0.4
43	0.97	0.1	9.33	1.0
44	1			

Number of observations: 11,364



Note. Data source: BiB - analysis cohort - up to and including Year 7

Figure 105 - Odds ratio (with 95% confidence intervals) of SEND from logistic regression, each week of gestation is a separate category, compared to 40 weeks

Categorising gestational age groups and comparing to full term reference category

This is a practical way of modelling gestational age and developmental disorder, which fits the data. Compared to developmental disorder the effect of gestational age is smaller and is only just statistically significant in the early term (37-38 weeks) group.

Table 113 - Odds ratio of Special Educational Needs and Disabilities from logistic regression, with gestational age categories, compared to full term reference category

Gestational age category	Odds ratio	95% conf. interval		P value
<34 weeks	2.00	1.47	2.72	<0.001
34 - 36 weeks	1.63	1.36	1.97	<0.001
37 - 38 weeks	1.11	1.00	1.23	0.04
39-41 weeks	1.00 (reference)			
>41 weeks	1.12	0.78	1.61	0.5

Number of observations = 11 ,368

Appendix 5.14. Modelling incidence rate of Special Educational Needs and Disabilities (SEND)

An exploratory analysis was carried out to see if similar results would be obtained if incidence rate of SEND were modelling instead of cumulative incidence.

Table 114 - Incidence rate ratios of developmental disorder from Poisson regression, with gestational age categories, compared to full term reference category

	Incidence rate ratio	95% confidence interval		P-value
<34 weeks	1.68	1.33	2.14	<0.001
34-36 weeks	1.49	1.29	1.73	<0.001
37-38 weeks	1.08	1.00	1.18	0.07
39-41 weeks	1.00 (reference)			
>41 weeks	1.09	0.80	1.48	0.6

Number of observations 13,172

A test for overdispersion was carried out using the *overdisp* command. The t test of the coefficient of û indicates the non-equi dispersion (i.e. overdispersion) (p <0.001), thus favouring negative binomial regression (Fávero et al., 2020). The results of the negative binomial regression are shown below.

Table 115 - Incidence rate ratios of developmental disorder from negative binomial regression, with gestational age categories, compared to full term reference category

	Incidence rate ratio	95% confidence interval		P value
<34 weeks	1.68	1.33	2.14	<0.001
34 - 36 weeks	1.49	1.29	1.73	<0.001
37 - 38 weeks	1.08	1.00	1.18	0.07
39-41 weeks	1.00 (reference)			
>41 weeks	1.09	0.80	1.48	0.6

Number of observations = 13,144

The incidence rate ratios are similar to the odds ratios from the final logistic regression model. Therefore, for simplicity and ease of interpretation, logistic regression, using five gestational age categories as described, was used for all remaining analyses.

Appendix 5.15. Modelling cumulative incidence of SEND and gestational age – complete case analysis

A complete case analysis was carried out. The results are very similar to the final adjusted imputed model.

Table 116 - Results of logistic regression model including all covariates of interest, odds ratio of Special Educational Needs and Disability by gestational age.

	Odds ratio	**95% confidence interval**		**P value**
Gestational age				
<34 weeks	2.11	1.44	3.10	<0.001
34 - 36 weeks	1.66	1.32	2.10	<0.001
37 - 38 weeks	1.15	1.02	1.30	0.02
39-41 weeks	1.00 (reference)			
>41 weeks	1.17	0.78	1.74	0.4
Child's sex				
Male	2.26	2.05	2.50	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.36	1.19	1.56	<0.001
Maternal age (in years) at child's delivery				
<21	1.24	1.02	1.50	0.03
21-25	1.21	1.04	1.40	0.01
26-30	1.09	0.94	1.26	0.2
31-35	1.00 (reference)			
>35	1.12	0.92	1.35	0.3
Socio-economic position - Five group latent class analysis				
Least deprived	1.00 (reference)			
Employed not mat deprived	1.01	0.85	1.21	1.0
Employed no access to money	1.44	1.20	1.72	<0.001
Benefits but coping	2.05	1.75	2.39	<0.001
Most deprived	2.48	2.09	2.95	<0.001
Ethnicity				
White	1.22	1.08	1.38	0.001
Mixed	0.89	0.71	1.12	0.3
Asian	1.00 (reference)			
Black	1.05	0.69	1.59	0.8
Other	0.51	0.28	0.93	0.03
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.06	0.91	1.22	0.5

Number of observations: 9,084. Global p-values shown for variables with multiple categories.

Appendix 5.16. Model diagnostics: SEND from education records (complete case analysis)

Goodness-of-fit tests are not directly applicable to multiple imputation results (StataCorp, nd.). Therefore, the model diagnostics were carried out on the complete case analysis (appendix 5.15). Goodness of fit, model discrimination and influential covariate patterns and outliers were investigated, but the results of which did not require changes to be made to the model.

Goodness of fit

Hosmer-Lemeshow goodness-of-fit test showed a $\chi 2 = 5.04$, p-value = 0.8, indicating a good fit.

Model discrimination

A graph showing sensitivity and specificity of the model was produced, as shown below. This shows that the optimal probability cut off is 0.265. Using a cut-off of 0. 265 the model would correctly classify 61.3 % of children.

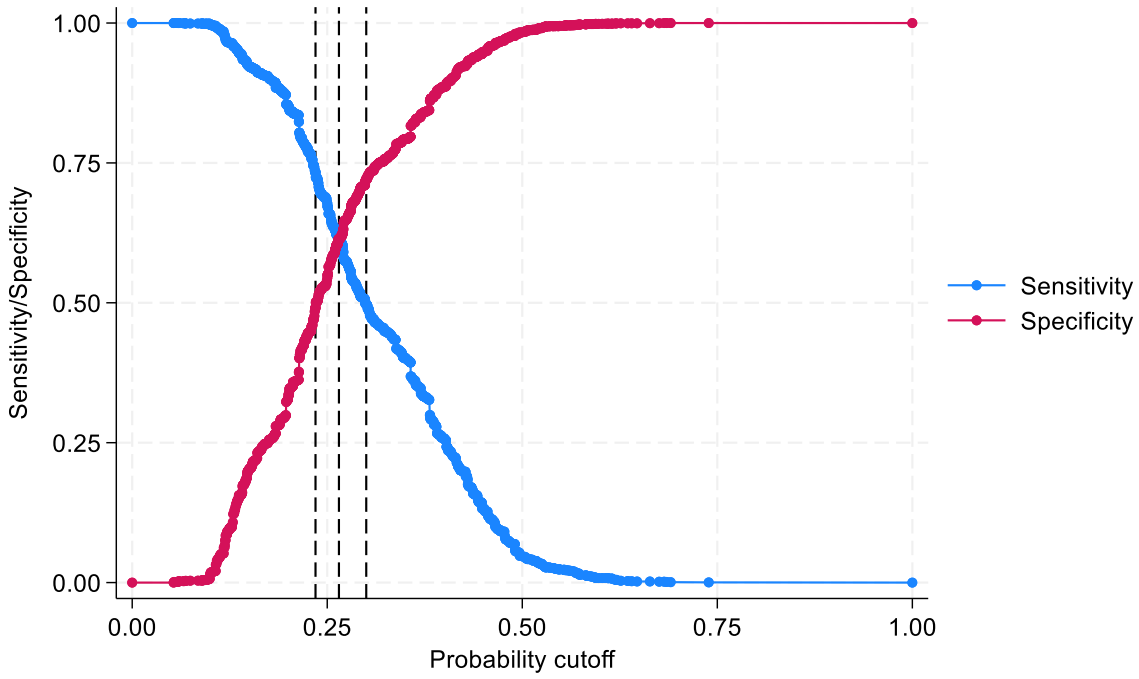


Figure 106 - Sensitivity and specificity of gestational age and SEND model versus probability cut off.

Dotted lines indicate probabilities of 0.235, 0.265, 0.30

A receiver operating characteristic curve (ROC curve) was plotted. This showed an area under the curve (AUC) of 0.66, see Figure 107 below.

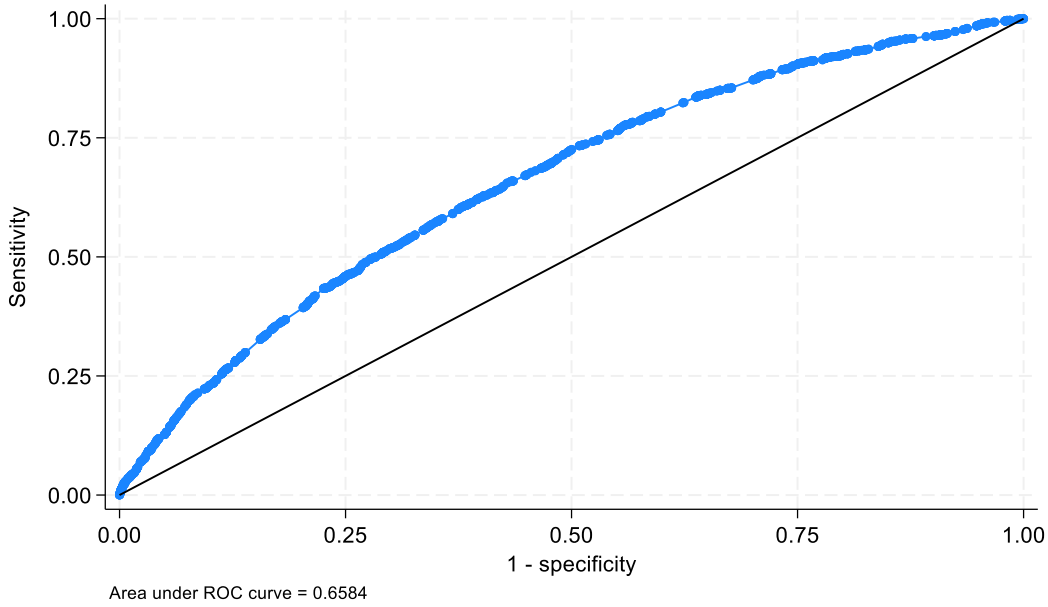


Figure 107 - Receiver operating characteristic (ROC) curve for gestational age and SEND model

Influential Covariate patterns

Pregibon's delta beta influence statistic was plotted. The change in Pearson chi-square statistic when an observation is removed was plotted. Covariate pattern 5 appeared slightly separated from the bulk of the other patterns and so was removed from the regression and it was re-run, see Table 117. Only two participants had this covariate pattern, and the estimates were not changed substantially when the covariate pattern was removed.

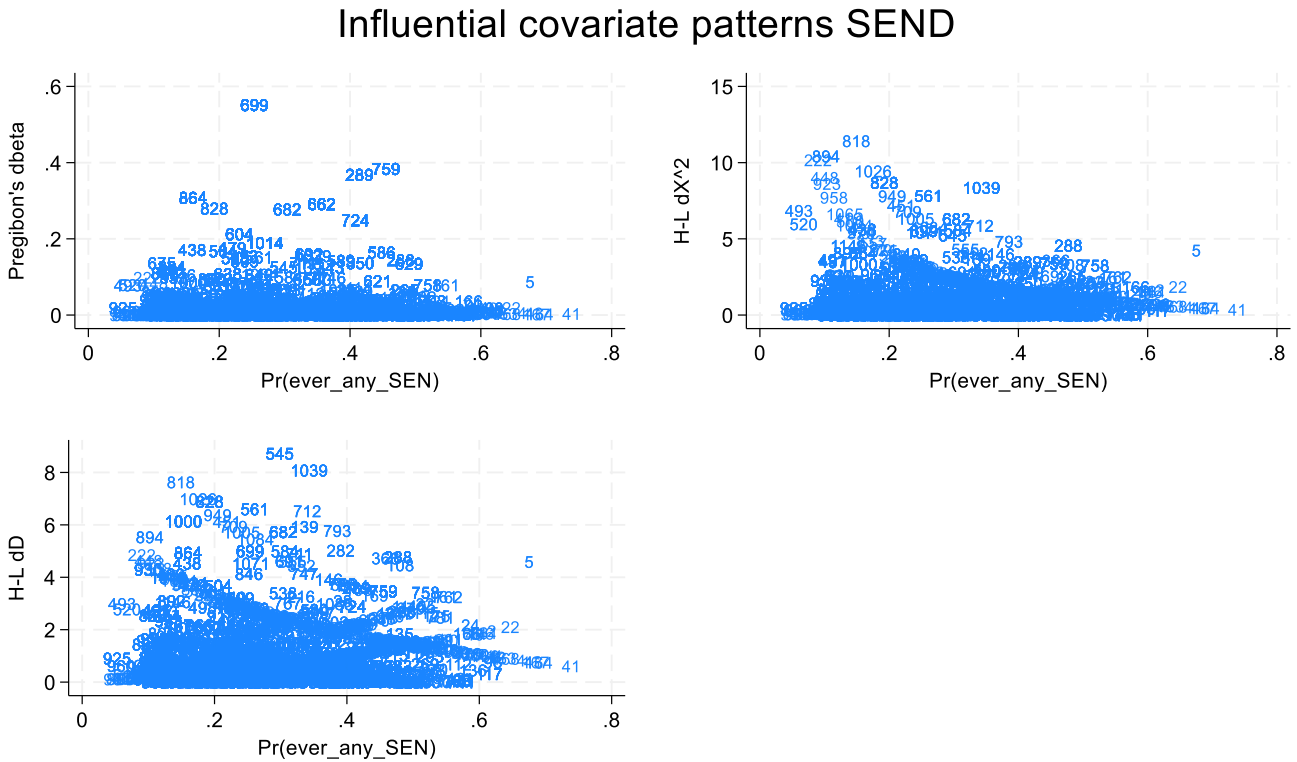


Figure 108 - Pearson's Residuals, Standardised Pearson's Residuals and Deviance Residuals plotted against probability of Special Educational Needs and Disabilities (SEND)

Table 117 - Results of logistic regression model, association of gestational age with SEND excluding covariate patten 5

	Odds ratio	95% confidence interval		P value
Gestational age				
<34 weeks	2.22	1.51	3.26	<0.001
34 - 36 weeks	1.66	1.31	2.10	<0.001
37 - 38 weeks	1.15	1.02	1.30	0.02
39-41 weeks	1.00 (reference)			
>41 weeks	1.17	0.78	1.74	0.4
Child's sex				
Male	2.27	2.05	2.50	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.36	1.189	1.557	<0.001
Maternal age (in years) at child's delivery				
<21	1.24	1.02	1.50	0.03
21-25	1.21	1.04	1.40	0.01
26-30	1.09	0.94	1.26	0.2
31-35	1.00 (reference)			
>35	1.12	0.92	1.35	0.3
Socio-economic position - Five group latent class analysis				
Least deprived	1.00 (reference)			
Employed not mat deprived	1.01	0.85	1.20	0.9
Employed no access to money	1.44	1.20	1.72	<0.001
Benefits but coping	2.04	1.75	2.39	<0.001
Most deprived	2.48	2.09	2.95	<0.001
Ethnicity				
White	1.22	1.08	1.38	0.001
Mixed	0.89	0.71	1.12	0.3
Asian	1.00 (reference)			
Black	1.05	0.69	1.59	0.8
Other	0.51	0.28	0.93	0.03
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.06	0.92	1.22	0.5

Number of observations: 9,082

Influential Outliers

Pearson's residuals, standardised Pearson's residuals and deviance residuals were plotted, see Figure 109 below. This showed covariate pattern 41 and 5 could be an outlier as it slightly removed from the bulk of the other points in all three graphs. The regression was repeated excluding covariate pattern 41, which gave the results shown in Table 118. Exclusion of this covariate pattern reduced the odds ratio for the <34 week group slightly. All other results remained essentially unchanged.

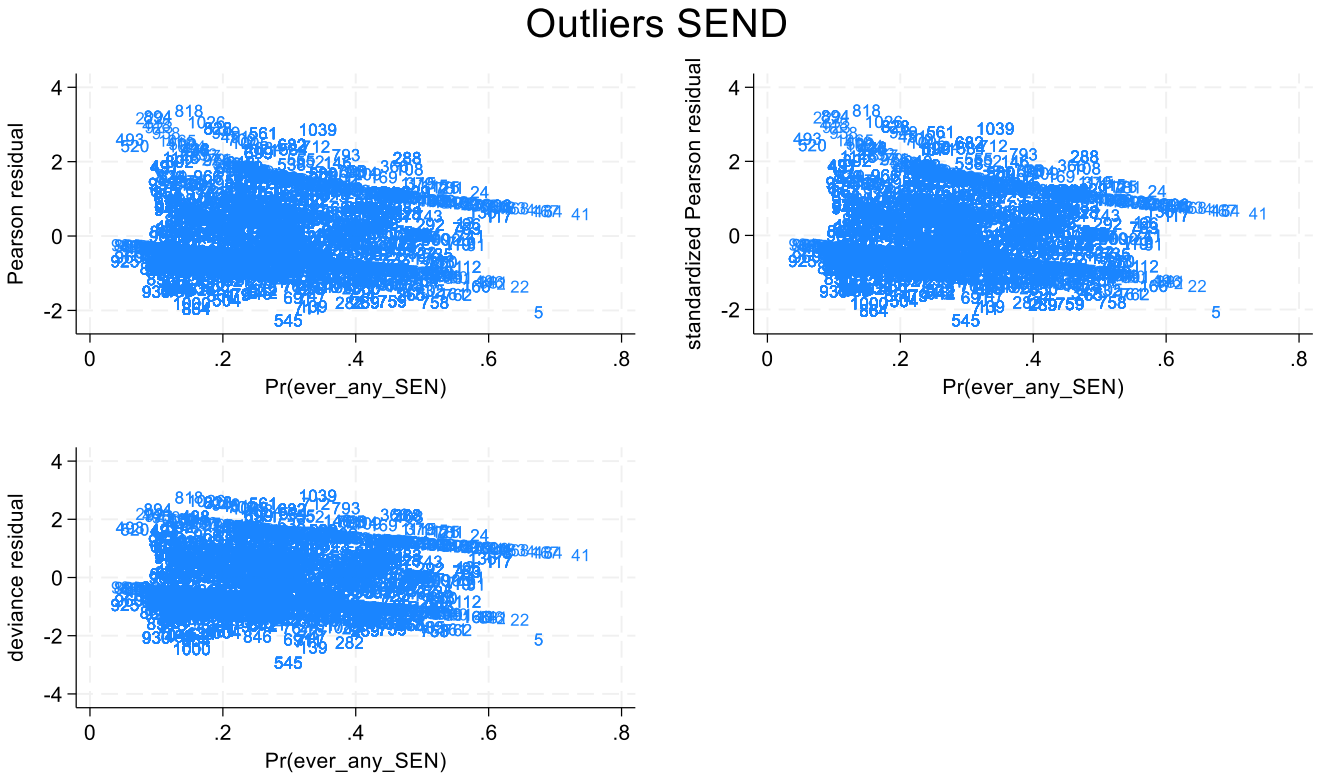


Figure 109 - Pearson's residuals, standardised Pearson's residuals and deviance residuals plotted against probability of special educational needs and disabilities (SEND)

Table 118 - Results of logistic regression model, association of gestational age with SEND, excluding covariate patten 41, a potential outlier

	Odds ratio	**95% confidence interval**		**P value**
Gestational age				
<34 weeks	2.09	1.42	3.07	<0.001
34 - 36 weeks	1.66	1.31	2.10	<0.001
37 - 38 weeks	1.15	1.02	1.30	0.02
39-41 weeks	1.00 (reference)			
>41 weeks	1.17	0.78	1.74	0.4
Child's sex				
Male	2.26	2.05	2.49	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.36	1.19	1.56	<0.001
Maternal age (in years) at child's delivery				
<21	1.23	1.02	1.49	0.03
21-25	1.21	1.04	1.40	0.01
26-30	1.09	0.94	1.26	0.2
31-35	1.00 (reference)			
>35	1.12	0.92	1.35	0.3
Socio-economic position - Five group latent class analysis				
Least deprived	1.00 (reference)			
Employed not mat deprived	1.01	0.85	1.21	0.9
Employed no access to money	1.44	1.20	1.72	<0.001
Benefits but coping	2.05	1.75	2.39	<0.001
Most deprived	2.48	2.08	2.95	<0.001
Ethnicity				
White	1.22	1.08	1.38	0.001
Mixed	0.89	0.71	1.12	0.3
Asian	1.00 (reference)			
Black	1.05	0.69	1.59	0.8
Other	0.51	0.28	0.93	0.03
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.05	0.91	1.22	0.5

Number of observations: 9,083

Appendix 5.17. Alternative measure of socio-economic position, SEND

The complete case model was repeated using receipt of means tested benefits and maternal education as alternative measures of socio-economic position (SEP). The odds ratios for the gestational categories were largely unchanged. Also note the smaller number of observations (8,977 compared to 10,553 when the 5 group latent class measure of SEP is used).

Table 119 - Results of logistic regression model including all covariates of interest, odds ratio of SEND by gestational age, using alternative measure of socio-economic position. N = 8,977

	Odds ratio	**95% confidence interval**		**P value**
Gestational age				
<34 weeks	2.08	1.42	3.06	<0.001
34 - 36 weeks	1.70	1.34	2.15	<0.001
37 - 38 weeks	1.16	1.03	1.30	0.02
39-41 weeks	1.00 (reference)			
>41 weeks	1.12	0.75	1.68	0.6
Child's sex				
Male	2.20	2.00	2.43	<0.001
Female	1.00 (reference)			
Small for gestational age (SGA)				
Not SGA	1.00 (reference)			
SGA	1.38	1.21	1.58	<0.001
Maternal age (in years) at child's delivery				
<21	1.30	1.08	1.58	0.007
21-25	1.24	1.07	1.43	0.005
26-30	1.10	0.95	1.27	0.2
31-35	1.00 (reference)			
>35	1.10	0.90	1.33	0.4
Mother's highest educational qualification				
<5 GCSE equivalent	2.02	1.73	2.35	<0.001
5 GCSE equivalent	1.49	1.29	1.73	<0.001
A-level equivalent	1.21	1.02	1.44	0.03
Higher than A-level	1.00 (reference)			
other or foreign unknown	1.01	0.78	1.31	0.1
Receipt of means tested benefits (MTB)				
No MTB	1.00 (reference)			
MTB	1.32	1.19	1.46	<0.001
Maternal smoking				
No smoking	1.00 (reference)			
Smoking	1.09	0.95	1.26	0.2
Ethnicity				
White	1.11	0.99	1.25	0.07
Mixed	0.82	0.65	1.03	0.09
Asian	1.00 (reference)			
Black	1.16	0.76	1.77	0.5
Other	0.49	0.27	0.90	0.02

Appendix 5.18. Imputation: SEND and gestational age

Patterns of missingness

There were seven patterns of missingness (Table 120). The majority of these were seen in less than 1% of the analysis cohort. Child's sex and maternal age are not shown as they were complete.

Table 120 - Patterns of missingness. 0 = missing, 1 = non-missing

Percent of cohort	Ethnicity	Small for gestational age	Smoking	Socio-economic position - five group latent class analysis
80%	1	1	1	1
17%	1	1	0	0
2%	1	0	1	1
<1%	1	1	1	0
<1%	1	0	0	0
<1%	1	1	0	1
<1%	0	1	0	0
<1%	1	0	1	0
<1%	1	1	1	1

Selection of auxiliary variables

The same auxiliary variables were considered as with developmental disorder: pre-eclampsia, gestational diabetes (GDM), consanguinity, index of multiple deprivation (IMD) categories, and parity. A binary variable identifying missingness for each variable of interest with missing data was created. These identifier variables were regressed on the potential auxiliary variables to determine whether they were associated with missingness in the variables of interest.

Table 121 - Regression of missing small for gestational age (SGA) flag variable against potential auxiliary variables

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.32	0.20	0.51	<0.001
GDM	0.50	0.36	0.70	<0.001
Consanguinity	0.97	0.74	1.26	0.8
IMD category	0.89	0.78	1.02	0.09
Parity	0.87	0.89	1.06	0.5

Table 122 - Regression of missing 5 class latent class analysis flag variable against potential auxiliary variables

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.93	0.69	1.25	0.6
GDM	1.27	1.05	1.54	<0.001
Consanguinity	2.00	1.00	3.98	0.05
IMD category	1.44	0.96	2.18	0.08
Parity	0.88	0.85	0.90	<0.001

Table 123 - Regression of missing ethnicity flag variable against potential auxiliary variables

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.11	0.01	0.96	0.05
GDM	0.35	0.04	3.14	0.3
Consanguinity	Did not compute			
IMD categories	Did not compute			
Parity	0.76	0.48	1.20	0.23

Table 124 - Regression of missing Smoking flag variable against potential auxiliary variables

	Odds ratio	**95% confidence intervals**		**p value**
Pre-eclampsia	0.91	0.67	1.22	0.5
GDM	1.29	1.07	1.57	0.01
Consanguinity	0.67	0.27	1.66	0.4
IMD quintiles	0.94	0.58	1.45	0.7
Parity	0.87	0.84	0.90	<0.001

Pre-eclampsia, gestational diabetes, and maternal parity were associated with the odds of missingness in at least one of the covariates or interest. Therefore, they were included in the imputation as auxiliary variables. Twenty five imputations were carried out as this exceeds the overall percentage of missing data (White et al., 2011). The imputations were carried out according to the type of variable, as follows:

- Logistic regression:
    - Gestational diabetes
    - Pre-eclampsia
    - Small for gestational age
    - Smoking
- Multinomial logistic regression
    - Ethnicity
- Ordered logistic regression
    - 5 group latent class analysis
    - Parity

Appendices

Imputation diagnostics

The distributions of the imputed, observed, and overall values were compared. The proportion in each category in the final (completed) dataset (containing imputed and observed values).

Table 125 - Imputed, observed, and final (completed) values. Special Educational Needs and Disabilities.

	Observed	**Imputed**	**Completed**
Ethnicity			
White	36.5%	66.7%	36.6%
Mixed	5.7%	0.0%	5.6%
Asian	55.0%	33.3%	55.0%
Black	1.5%	0.0%	1.5%
Other	1.4%	0.0%	1.4%
Small for Gestational Age (SGA)			
not SGA	85.8%	87.5%	85.9%
SGA	14.2%	12.5%	14.1%
Smoking in pregnancy			
no smoking	83.5%	83.2%	83.4%
smoking	16.5%	16.8%	16.6%
Socio-economic position – 5 group latent class analysis			
Least deprived and most educated	17.6%	13.8%	17.0%
Employed not materially deprived	19.7%	16.9%	19.2%
Employed no access to money	15.4%	15.0%	15.3%
Benefits but coping	30.7%	34.7%	31.4%
Most deprived	16.5%	19.7%	17.1%

Appendix 5.19. Stratified analysis – complete case analysis

Table 126 - Results of logistic regression model for developmental disorder stratified by two largest ethnic groups – Complete case analysis

	Asian children N = 5,530				White children N = 4,162			
	Odds ratio	95% confidence interval		P value	Odds ratio	95% confidence interval		P value
Gestational age								
<34 weeks	3.21	1.85	5.58	<0.0001	1.55	0.78	3.06	0.2
34 - 36 weeks	1.61	1.07	2.42	0.02	1.22	0.78	1.89	0.4
37 - 38 weeks	1.26	1.04	1.54	0.02	1.12	0.88	1.43	0.4
39-41 weeks	1.00 (reference)							
>41 weeks	1.8	0.9	3.63	0.1	1.6	0.88	2.91	0.1
Child's sex								
Female	1.00 (reference)							
Male	1.89	1.59	2.26	<0.0001	2.56	2.09	3.14	<0.0001
Small for gestational age (SGA)								
Not SGA	1.00 (reference)							
SGA	1.32	1.07	1.62	0.01	1.08	0.78	1.49	0.7
Maternal age category								
<21	0.91	0.59	1.4	0.7	0.86	0.6	1.23	0.4
21-25	1.06	0.83	1.37	0.6	1.13	0.84	1.52	0.4
26-30	1.03	0.81	1.32	0.8	0.98	0.72	1.33	0.9
31-35 weeks	1.00 (reference)							
>35	1.41	1.03	1.94	0.03	1.44	1	2.08	0.05
Socio-economic position								
Most educated, least deprived	1.00 (reference)							
Employed not materially deprived	1.4	1.02	1.93	0.04	1.23	0.88	1.71	0.2
Employed no access to money	1.23	0.91	1.66	0.2	1.73	1.2	2.5	0.003
Benefits but coping	1.27	1	1.62	0.05	2.26	1.56	3.27	<0.0001
Most deprived	1.11	0.81	1.53	0.5	2.34	1.62	3.37	<0.0001
Maternal smoking during pregnancy								
non-smoking	1.00 (reference)							
Smoking (any)	1.14	0.73	1.78	0.6	1.05	0.84	1.3	0.7

Table 127 - Results of logistic regression model for Special Educational Needs and Disabilities stratified by two largest ethnic groups – Complete case analysis

	White children n = 3,427				**Asian children N = 4,931**			
	Odds ratio	95% confidence interval		P value	Odds ratio	95% confidence interval		P value
Gestational age								
<34 weeks	1.30	0.69	2.47	0.4	3.18	1.90	5.34	<0.0001
34 - 36 weeks	1.71	1.19	2.47	0.004	1.73	1.24	2.41	0.001
37 - 38 weeks	1.08	0.88	1.32	0.5	1.18	1.01	1.37	0.03
39-41 weeks	1.00 (reference)							
>41 weeks	1.40	0.80	2.44	0.2	1.13	0.61	2.11	0.7
Child's sex								
Female	1.00 (reference)							
Male	2.47	2.10	2.90	<0.0001	2.21	1.93	2.52	<0.0001
Small for gestational age (SGA)								
Not SGA	1.00 (reference)							
SGA	1.17	0.90	1.53	0.2	1.39	1.18	1.63	<0.0001
Maternal age category								
<21	1.07	0.80	1.42	0.7	1.48	1.09	2.01	0.01
21-25	1.07	0.83	1.37	0.6	1.25	1.03	1.51	0.02
26-30	0.96	0.75	1.23	0.8	1.15	0.96	1.38	0.1
31-35 weeks	1.00 (reference)							
>35	1.21	0.89	1.65	0.2	1.08	0.84	1.40	0.5
Socio-economic position								
Most educated, least deprived	1.00 (reference)							
Employed not materially deprived	1.11	0.85	1.45	0.5	1.04	0.79	1.37	0.8
Employed no access to money	1.58	1.17	2.14	0.003	1.39	1.09	1.77	0.008
Benefits but coping	2.61	1.92	3.55	<0.0001	1.92	1.58	2.34	<0.0001
Most deprived	2.92	2.16	3.94	<0.0001	2.18	1.72	2.77	<0.0001
Maternal smoking during pregnancy								
non-smoking	1.00 (reference)							
Smoking (any)	1.05	0.88	1.26	0.6	0.90	0.63	1.30	0.6

Appendix 5.20. Stratified analysis – imputation diagnostics

Table 128 - Multiple imputation chained equations diagnostics for analyses stratified by ethnicity.

	Asian children.			White children.		
	Developmental disorder					
	observed	imputed	completed	observed	imputed	completed
Socio-economic position						
n	5691	1279	6970	4268	733	5001
Least dep most educated	0.204	0.195	0.202	0.172	0.121	0.164
Employed not mat deprived	0.103	0.109	0.104	0.331	0.307	0.328
Emplyd no access to money	0.146	0.142	0.145	0.156	0.157	0.156
Benefits but coping	0.415	0.421	0.416	0.158	0.173	0.16
Most deprived	0.131	0.134	0.132	0.183	0.241	0.191
Smoking during pregnancy						
n	5696	1274	6970	4279	722	5001
no smoking	0.966	0.958	0.965	0.681	0.593	0.668
smoked	0.034	0.042	0.035	0.319	0.407	0.332
Small for gestational age (SGA)						
n	6805	165	6970	4888	113	5001
not SGA	0.821	0.800	0.821	0.907	0.947	0.908
SGA	0.179	0.200	0.179	0.093	0.053	0.092
	Special Educational Needs and Disabilities					
Socio-economic position						
n	5129	1185	6314	3562	636	4198
Least dep most educated	0.186	0.183	0.185	0.159	0.123	0.153
Employed not mat deprived	0.105	0.086	0.101	0.334	0.299	0.328
Emplyd no access to money	0.146	0.167	0.15	0.159	0.148	0.157
Benefits but coping	0.426	0.42	0.425	0.16	0.181	0.163
Most deprived	0.137	0.143	0.138	0.189	0.25	0.198
Smoking during pregnancy						
n	5131	1183	6314	3571	627	4198
no smoking	0.967	0.954	0.965	0.668	0.611	0.659
smoked	0.033	0.046	0.035	0.332	0.389	0.341
Small for gestational age (SGA)						
n	6165	149	6314	4094	104	4198
not SGA	0.818	0.826	0.819	0.908	0.913	0.908
SGA	0.182	0.174	0.181	0.092	0.087	0.092

Appendix 5.21 Missing General Health Questionnaire-28 (GHQ-28) score by ethnicity

Table 129 - Missing General Health Questionnaire-28 (GHQ-28) score by ethnicity

	White	Mixed	Asian	Black	Other	missing	Total
n missing	1,318	205	2,306	75	77	72	4,053
% missing	26.4	29.1	33.1	30.6	43.0	98.6	30.8
Total	5,001	704	6,970	245	179	73	13,172

Appendix 6.1. Three class model, for comparison

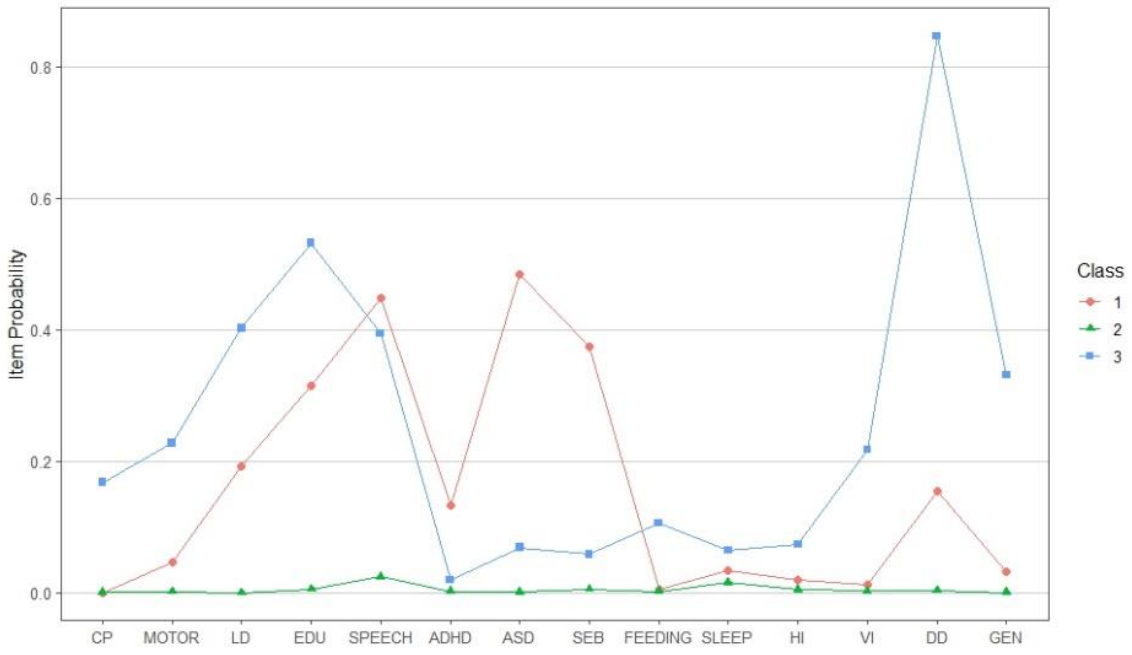


Figure 110 - Profile plot of three class model

CP: Cerebral palsy; MOTOR: motor function problems; LD: Learning disability/Intellectual disability; EDU: Education problem; SPEECH: Speech, language and communication disorders; ADHD: Hyperactivity, impulsivity, and inattention, including Attention Deficit Hyperactivity Disorder (ADHD); ASD: Autism spectrum disorder; SEB: Social, emotional, and behavioural problems; FEEDING: feeding problems; SLEEP: sleep apnoea; HI: hearing impairment; VI: visual impairment; DD: developmental delay; GEN: general developmental disorder. (N = 13,172).NB, There were no codes in participants' records corresponding to Executive function problems.

Appendix 6.2. Distribution of characteristics by latent class

*Table 130 - Distribution of cohort characteristics by class membership. *Data was supressed*

	Group 1 – "Typical development"	Group 2 – "Educational difficulties"	Group 3 – "Social, emotional, behavioural & communication difficulties"	Group 4 – "Early dev. impairment, with physical & intellectual disabilities"	Total
Gestational age					
<34 weeks	190	12	*	*	214
	1.5%	3.5%			1.6%
34-36 weeks	569	22	*	*	606
	4.5%	6.3%			4.6%
37-38 weeks	2,786	94	47	23	2,950
	22.2%	27.1%	24.9%	23.0%	22.4%
39-41 weeks	8,823	212	128	59	9,222
	70.4%	61.1%	67.7%	59.0%	70.0%
>41 weeks	168	*	*	*	180
	1.3%	*	*	*	1.4%
Total	12,536	347	189	100	13,172
	100%	100%	100%	100%	100%
Sex					
male	6,357	223	159	62	6,801
	50.7%	64.3%	84.1%	62.0%	51.6%
female	6,179	124	30	38	6,371
	49.3%	35.7%	15.9%	38.0%	48.4%
Total	12,536	347	189	100	13,172
	100%	100%	100%	100%	100%
Multiplicity					
singleton	12,247	335	*	*	12,867
	97.7%	96.5%			97.7%
twin	289	12	*	*	305
	2.3%	3.5%			2.3%
Total	12,536	347	189	100	13,172
	100%	100%	100%	100%	100%
Small for gestational age (SGA)					
not SGA	10,557	268	165	77	11,067
	86.2%	80.0%	89.2%	77.0%	86.0%
SGA	1,685	67	20	23	1,795
	13.8%	20.0%	10.8%	23.0%	14.0%
Total	12,242	335	185	100	12,862
	100%	100%	100%	100%	100%
Maternal age at delivery (years)					
<21	1,268	31	24	11	1,334
	10.1%	8.9%	12.7%	11.0%	10.1%
21-25	3,618	100	51	29	3,798
	28.90%	28.8%	27.0%	29.0%	28.8%

	Group 1 – "Typical development"	Group 2 – "Educational difficulties"	Group 3 – "Social, emotional, behavioural & communication difficulties"	Group 4 – "Early dev. impairment, with physical & intellectual disabilities"	Total
26-30	4,000	110	60	31	4,201
	31.9%	31.7%	31.8%	31.0%	31.9%
31-35	2,436	63	27	19	2,545
	19.4%	18.2%	14.3%	19.0%	19.3%
>35	1,214	43	27	10	1,294
	9.7%	12.4%	14.3%	10.0%	9.8%
Total	12,536	347	189	100	13,172
	100%	100%	100%	100%	100%
Smoking during pregnancy					
Smoking	1,693	49	*	*	1,782
	16.4%	16.7%			16.4%
No smoking	8,659	244	*	*	9,103
	83.7%	83.3%			83.6%
Total	10,352	293	157	83	10,885
	100%	100%	100%	100%	100%
Ethnicity					
White	4,749	136	94	22	5,001
	38.1%	39.2%	49.7%	22.0%	38.2%
Mixed	671	*	18	*	704
	5.4%		9.5%		5.40%
Asian	6,633	194	71	72	6,970
	53.2%	55.9%	37.6%	72.0%	53.2%
Black	234	*	*	*	245
	1.90%				1.9%
Other	176	*	*	*	179
	1.4%				1.4%
Total	12,463	347	189	100	13,099
	100%	100%	100%	100%	100%
Socio-economic position					
Least deprived	2,016	37	33	*	2,096
	19.6%	12.7%	21.0%		19.3%
Employed not deprived	2,070	47	37	*	2,160
	20.1%	16.2%	23.6%		19.9%
Employed no access to money	1,574	34	30	18	1,656
	15.3%	11.7%	19.1%	22.0%	15.3%
Benefits but coping	3,023	112	31	35	3,201
	29.3%	38.5%	19.8%	42.7%	29.5%
Most deprived	1,630	61	26	13	1,730
	15.8%	21.0%	16.6%	15.9%	16.0%
Total	10,313	291	157	82	10,843
	100	100	100	100	100

Appendix 6.3. Complete case analysis of multinomial adjusted logistic regression

Table 131 - Relative risk ratio (RRR) of class membership, according to gestational age category. Group 1 – "Typical development" is reference class.

	RRR	**95% confidence interval**		**P value**	**RRR**	**95% confidence interval**		**P value**	**RRR**	**95% confidence interval**		**P value**
	Group 2 – "Educational difficulties"				**Group 3 – "Social, emotional, behavioural & communication difficulties"**				**Group 4 – "Early developmental impairment, with physical & intellectual disabilities"**			
Gestational age categories												
<34 weeks	2.26	1.03	4.93	0.04	0.49	0.07	3.54	0.5	9.21	4.04	20.98	<0.0001
34-36 weeks	1.56	0.91	2.68	0.1	1.09	0.5	2.38	0.8	2.1	0.83	5.32	0.1
37-38 weeks	1.44	1.09	1.9	0.01	1.14	0.77	1.69	0.5	1.27	0.74	2.17	0.4
39-41 weeks	1.00 (ref)											
>41 weeks	2.02	0.93	4.41	0.08	1.22	0.38	3.92	0.7	2.22	0.53	9.35	0.3
Child's sex												
female	1.00 (ref)											
male	1.72	1.34	2.2	<0.0001	4.94	3.21	7.61	<0.0001	1.5	0.96	2.35	0.07
Small for gestational age (SGA)												
Not SGA	1.00 (ref)											
SGA	1.54	1.13	2.11	0.007	0.9	0.53	1.5	0.7	1.77	1.04	3	0.04
Maternal age (years)												
<21	0.64	0.38	1.1	0.1	1.91	1.01	3.61	0.046	1.14	0.44	2.93	0.8
21-25	1.04	0.73	1.49	0.8	1.48	0.87	2.52	0.2	1.23	0.63	2.4	0.5
26-30	1.03	0.72	1.46	0.9	1.37	0.81	2.3	0.2	1.17	0.61	2.25	0.6
31-35	1.00 (ref)											
>35	1.34	0.87	2.09	0.2	1.92	1.03	3.56	0.04	1.35	0.58	3.14	0.5

	RRR	95% confidence interval		P value	RRR	95% confidence interval		P value	RRR	95% confidence interval		P value
	Group 2 – "Educational difficulties"				Group 3 – "Social, emotional, behavioural & communication difficulties"				Group 4 – "Early developmental impairment, with physical & intellectual disabilities"			
Maternal smoking												
No smoking	1.00 (ref)											
smoking	0.92	0.64	1.32	0.6	1.00 (ref)				1.00 (ref)			
Socio-economic position												
least deprived and most educated	1.00 (ref)											
Employed, not materially deprived	1.18	0.75	1.85	0.5	1.01	0.61	1.66	0.98	0.68	0.24	1.9	0.5
Employed, no access to money	1.25	0.77	2.01	0.4	1.16	0.69	1.96	0.6	2.59	1.19	5.67	0.02
Benefits not materially deprived	2.11	1.42	3.14	<0.0001	0.68	0.4	1.15	0.1	2.25	1.09	4.63	0.03
Most economically deprived	2.21	1.43	3.42	<0.0001	0.89	0.5	1.57	0.7	2.05	0.88	4.76	0.1
Ethnicity												
White	1.00 (ref)											
Mixed	0.49	0.24	1.02	0.06	1.07	0.56	2.04	0.8	1.44	0.48	4.33	0.5
Asian	0.78	0.58	1.06	0.1	0.72	0.48	1.06	0.1	1.46	0.8	2.67	0.2
Black	0.89	0.35	2.24	0.8	1.29	0.46	3.63	0.6	0.79	0.1	6.1	0.8
Other	0.29	0.04	2.14	0.2	0.47	0.06	3.45	0.5	0	0	1.2e+307	0.98

N = 10,553.

Appendix 6.4. Multinomial regression – imputation diagnostics

Table 132 - Imputed, observed, and final (completed) values.

	Observed	Imputed	Completed
Small for gestational age (SGA)			
n	12,862	310	13,172
not SGA	0.86	0.91	0.862
SGA	0.14	0.09	0.138
Smoking			
n	10,885	2,287	13,172
no smoking	0.836	0.842	0.837
smoking	0.164	0.158	0.163
Socio-economic position			
n	10,843	2,329	13,172
least deprived and most educated	0.193	0.178	0.191
Employed, not materially deprived	0.199	0.186	0.197
Employed, no access to money	0.153	0.154	0.153
Benefits not materially deprived	0.295	0.31	0.298
Most economically deprived	0.16	0.173	0.162
ethnicity			
n	13,099	73	13,172
White	0.382	0.384	0.382
Mixed	0.054	0.055	0.054
Asian	0.532	0.562	0.532
Black	0.019	0	0.019
Other	0.014	0	0.014

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike Information Criterion
AUC	Area under curve
aRRR	Adjusted Relative Risk Ratios
ASD	Autism spectrum disorder
BiB	Born in Bradford
BIC	Bayesian Information Criterion
BRIEF-P	Behaviour Rating Inventory of Executive Function–Preschool Version
CAIC	Consistent Akaike Information Criterion
CBCL	Child Behaviour Checklist
CDC	Child development centre
CI	Confidence interval
CPRS-R:S	Conners Parent Rating Scale–Revised
CTRS-RSF	Conners Teacher Rating Scale–Revised Short Form
CTV2/3	Clinical terms version 2/3
DCD	Developmental coordination disorder
DD	Developmental delay
DF	Degrees of freedom
ECLS-B	Early Childhood Longitudinal Studies Program Birth cohort
FMI	Fraction of missing information
GDDS	Gesell Development Diagnosis Scale
GDM	Gestational diabetes mellitus
GP	General Practitioner
HSCS-PS	Health Status Classification System Preschool Version
ICD	International classification of diseases
IDS	Intelligence and Development Scales
IMD	Index of Multiple Deprivation
IVH	Intraventricular haemorrhage
LCA	Latent class analysis
LGA	Large for gestational age
LMP	Last menstrual period
LoliPOP	Longitudinal Preterm Outcome Project
MA	Meta analysis
MAR	Missing at Random

MCAR	Missing Completely at Random
M-CHAT	Modified Checklist for Autism in Toddlers
MCS	Millenium cohort study
MICE	Multiple Imputation with Chained Equations
MNAR	Missing Not at Random
MTB	Means tested benefits
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
PPROM	Preterm premature rupture of membranes
PVL	Periventricular leucomalacia
RE	Relative efficiency
ROC	Receiver operating characteristic
ROP	Retinopathy of Prematurity
RRR	Relative Risk Ratios
RVI	Relative increase in variance
SABIC	Sample-size adjusted Bayesian Information Criterion
SBQ	Social Behavior Questionnaire
SCBU	Special care baby unit
SD	Standard deviation
SDQ	Strengths and difficulties questionnaire
SE	Standard error
SEND	Special educational needs and disabilities
SEP	Socio-economic position
SGA	Small for gestational age
UK	United Kingdom
USA	United States of America
VIF	Variance Inflation Factor

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