

**Seizure disorders, socioeconomic position, pregnancy and obstetric complications and the development of behavioural problems in children:  
Findings from a British birth cohort**

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## **Abstract**

### **Background**

The development of both seizure disorders and behavioural problems can be predicted by low socioeconomic position or pregnancy and obstetric complications. Additionally, there is evidence for an association between seizure disorders and the development of behavioural problems. It is unclear if the effect of lower socioeconomic position and obstetric or pregnancy complications on the development of behavioural problems in children with a history of seizure disorders occurs directly (independent of seizures) or indirectly (dependent on seizures).

### **Methods**

This analysis follows up to 16 years, the 17,416 children out of a total of 18,558 children born in the first week of March, 1958 in Britain. Logistic regression measures were used to determine if factors of low socioeconomic position or pregnancy and obstetric complications predicted the development of seizure disorders and behavioural problems at 7 years (first survey), 11 years (second survey) and 16 years (third survey). The direct effect (independent of seizures) and indirect effect pathways (dependent of seizures) of developing behavioural problems in children disadvantaged by low socioeconomic position or pregnancy and obstetric complications were estimated using logistic regression methods.

### **Results**

Most factors of low socioeconomic position and pregnancy and obstetric complications investigated, consistently predicted the development of behavioural problems across the surveys. Similarly, most factors of socioeconomic position (except single marital status) and pregnancy and obstetric complications (especially

low birthweight and pre-eclampsia) were each associated with seizure disorders in one or more surveys. Seizure disorders including epilepsy were associated with behavioural problems at most of the surveys. Behavioural problems (at 16 years) in children who had been disadvantaged by low socioeconomic position or pregnancy factors, occurred mainly through the direct effect pathway (independent of seizures) ( $p < 0.001$ ). However, they occurred through the indirect pathway (dependent on seizures) for children whose mothers were managed for pre-eclampsia (proportion of total effect mediated=2.8%,  $p = 0.047$ ). An indirect pathway was also suggested in those born with a low birthweight (proportion of total effect mediated=3.2%), but the evidence was weak.

### **Conclusions**

Most behavioural problems in children disadvantaged by socioeconomic position and pregnancy complications are not mediated by seizure disorders (i.e. occurs through a direct pathway). Seizure disorders however appear to mediate behavioural problems in pre-eclampsia and low birthweight (through an indirect pathway). Improvement of standards of living and maternal and child health may reduce the burden of psychiatric problems occurring through a direct pathway, while improved care of seizure disorders would help prevent those that occur through an indirect pathway.

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# Chapter 1: Introduction

## 1.1: Background

Social deprivation factors such as low social class, poor accommodation or financial difficulties; and obstetric or pregnancy factors such as low birthweight, pre-eclampsia, smoking during pregnancy or prematurity are associated with the development of both behavioural problems and seizure disorders, including epilepsy (Bor et al., 1993; Cannon et al., 2002; Lorant et al., 2007; Whitehead et al., 2006). Internalising behavioural problems such as anxiety and depression (Costello et al., 2003) and externalising behavioural problems such as conduct problems, oppositional defiant problems and attention-deficit/hyperactivity disorder (D'Onofrio et al., 2008) are common in children with epilepsy (Rodenburg et al., 2005). The proportion of behavioural problems in children with epilepsy is thought to be about 30%-50% (Davies et al., 2003a; Dunn et al., 2009). The relationship between seizure disorders and behavioural problems is thought to be bidirectional, although the mechanisms underlying this bi-directional association are still a subject of ongoing research. What is clear, is that seizure disorders can precede behavioural problems in children (Baki et al., 2004; Hesdorffer et al., 2007; Kanner, 2003). Although there are findings suggesting that behavioural problems such as depression can precede the onset of seizures (Kanner, 2006), the timing of the seizure disorders is still controversial, as there can be non-convulsive epileptiform discharges prior to the occurrence of behavioural problems. Furthermore, the documentation of the time of onset of seizures is dependent on the history from the patient or parents and may thus be somewhat unreliable. It is however unclear if the effect of lower socioeconomic position and obstetric or pregnancy complications on the

development of behavioural problems in children with a history of seizure disorders occurs directly (independent of seizures) or indirectly (dependent on seizures) (Mackinnon et al., 1995).

Neuropsychiatric problems have been extensively studied in epilepsy and recurrent seizure disorders (Agrawal and Govender, 2011; Austin et al., 2002), yet few studies have examined neuropsychiatric comorbidities in single and acute symptomatic seizures (Austin et al., 2002). It is now understood that psychopathology could be, in part, caused by epileptiform discharges, which are present even in both single seizure events and acute seizure disorders (Pressler et al., 2005). Additionally, behavioural problems have been recognised shortly before first recognised seizures which has suggested that chronic seizure disorders such as epilepsy could be pervasive disorders characterised by both seizures and behavioural problems (Austin et al., 2001). Furthermore, such single and acute seizures can result in a reactive process that in part increases the incidence of behavioural problems in children or even their parents (Austin et al., 2002; Pianta and Lothman, 1994). These findings support the assessment of neurobehavioural outcomes in virtually all seizure disorders, including those considered benign.

Studies investigating the neurobehavioural outcomes of seizure disorders other than epilepsy have yielded interesting results. One study that investigated all recurrent seizure events reported more behavioural problems in children who had experienced recurrent seizures compared to those who did not, controlling for demographics and use of anti-epileptic drugs (AEDs) (Austin et al., 2002). A study comparing behavioural problems between children with first recognised seizures and in those with asthma found more thought problems in those with epilepsy than in the

latter group (Austin et al., 2001). Even febrile seizures, which are thought to be benign, have very occasionally been associated with intellectual and behavioural problems. For example, febrile seizures occurring in children with pre-existing neurological and developmental impairments have been shown to worsen cognitive difficulties (Nelson and Ellenberg, 1978). Furthermore, the need for special schooling is greater in children who experience febrile seizures in the first year of life than in those who experience these seizures much later, suggesting that the timing of febrile seizures may be important in the association with behavioural or cognitive problems (Verity et al., 1998). This begs the important question if the behavioural status of children with any seizure disorder should be routinely assessed.

The mechanisms for the development of behavioural problems in seizure disorders have never been clear (Kanner, 2006). Some authors have asserted that behavioural problems are mainly caused through three mechanisms: (1) via an underlying neurological pathology that causes both seizures and behavioural problems (2) disruption of behaviour by seizure activity, and (3) children's negative psychological response to seizure activity (Austin et al., 2002). Evidence of behavioural problems in children before their first seizures has been recognized, and has been used to indicate the presence of underlying neurological problems (Austin et al., 2001). Other epilepsy related factors such as use of AEDs have also been suggested as important risk factors for particular behavioural problems (Banu et al., 2007).

Because low socioeconomic position and obstetric complications are thought to influence the development of both seizure disorders and behavioural problems, and because seizure disorders are also associated with behavioural problems, it is difficult to explain the role of seizure disorders in the causal pathway especially if

these factors have occurred together in the same child. Notwithstanding the fact that the relationship between the mentioned factors can be complicated further by the presence of cognitive impairment (Aldenkamp, 2006; Emerson et al.) and underlying genetic predispositions (Ottman et al., 1996), which possibly modify the encephalopathy that leads to the development of both seizure disorders and behavioural problems in children. Lack of understanding of how all these factors interact hinders effective prevention strategies for behavioural problems in children as it is unclear what proportion of the children disadvantaged by low socioeconomic position or obstetric complication have their behavioural problems occurring directly (independent of their seizure status) or indirectly through the seizures. No study has attempted to determine the indirect and direct causation pathway of behavioural problems in children disadvantaged by low socioeconomic position or obstetric complications early on in life and seizures disorders. There are, however, studies that have separately (but not together) investigated associations between (1) low socioeconomic position or obstetric complications and behavioural problems; and (2) seizure disorders and behavioural problems.

The direct and indirect effects of early life factors of socioeconomic position and obstetric or pregnancy complications on behavioural problems as explained by seizure disorders can be determined by mediation analysis (Mackinnon et al., 1995). The mediation analysis simply determines if the effects of lower socioeconomic position and obstetric or pregnancy complications on behavioural problems reduces when accounted for seizure disorders. In technical terms, the analysis decomposes or deconstructs total effect into direct and indirect effects (Buis, 2010; Erikson et al., 2005; Mackinnon et al., 1995), and in this analyses seizures will be treated as the mediating variables, with early life socioeconomic position and pregnancy

complications as the exposures and behavioural problems as the main outcome. The mediation analysis provides the strength of association for each pathway as well as the proportion of total effect mediated by seizures (Buis, 2010; Erikson et al., 2005). Such an analysis is possible when seizure disorders are an effect modifier rather than confounder and our intended analysis qualifies because in a cohort setting, both seizures disorders and behavioural problems would be predicted by early life low social-economic position or obstetric complications and not vice-versa (Buis, 2010). Furthermore, mediation analysis should only be used if the mediation variable (seizure disorders) is not caused by the outcome or dependent variable (behavioural problems) (Buis, 2010). To ensure these conditions are met, one should only include seizures that occurred before the development of behavioural problems in the mediation analysis. Some authors have felt that the mediator should be a biological factor rather than a social one, and seizures qualify because they are a biological condition (Baron and Kenny, 1986).

The analyses used data from the National Child and Development Study (NCDS). Data from the NCDS is available at United Kingdom data archive, University of Sussex, where data is available to all researchers. Permission to use the NCDS data was granted according to “an end user licence agreement- number SN 5565”, upon a commitment to adhere to all ethical requirements on data usage, distribution and safeguarding patient confidentiality.

## **1.2. Study hypothesis**

Using data from a nationally representative birth cohort from Britain, the following hypotheses were examined in children:

(1) Socioeconomic position and pregnancy/obstetric complications predict the development of behavioural problems.

(2) Socioeconomic position and pregnancy/obstetric complications predict the development of seizure disorders.

(3) Seizure disorders are associated with behavioural problems.

(4) Seizure disorders mediate a significant proportion of the total effect of the association between socioeconomic position or pregnancy complications and the behavioural problems.

## **Chapter 2 Literature review**

### **2.1. Synopsis of the search criteria**

All articles published in English were searched from PubMed using the following search terms and appropriate Boolean operators (1) (low socioeconomic position or poverty or low social class) and (seizures or epilepsy) (2) (obstetric factors or pregnancy factors) and (seizures or epilepsy) (3) (Epilepsy or seizures) and (behavioural problems or psychopathology or psychiatric problems or mental health problems) (4) (low socioeconomic position or poverty or low social class) and (behavioural problems or psychopathology or psychiatric problems or mental health problems) and (5) (obstetric factors or pregnancy factors) and (behavioural problems or psychopathology or psychiatric problems or mental health problems). Abstracts identified by the search were read and those deemed relevant to this analysis were included in the review. Also included in the literature review are those articles identified from the references of the papers that qualified for the literature review.

## **2.2. Socioeconomic position and seizure disorders**

An extensive body of knowledge has demonstrated an association between low socioeconomic status and a higher rate of hospital utilization and child morbidity (Bor et al., 1993). The direction of causality is difficult to determine since socioeconomic status may be both a consequence of epilepsy (Birbeck et al., 2007) or a risk factor for epilepsy (Elliott et al., 2009). It has been suggested that poverty is more likely to be a risk factor for epilepsy because in resource-limited countries the incidence of epilepsy is higher than that in the developed countries (Scott et al., 2001). Some studies did not find an association between the risk for epileptic seizures and poverty score or social class (Hackett' et al., 1987), while others found an association between deprivation and incident unprovoked seizures or epilepsy in adults but not children (Hesdorffer et al., 2005). These associations may be even more complicated considering that factors such as unemployment which may result from epilepsy (Morgan et al., 2000) and these are also important indices of deprivation and low social class (Carstairs and Morris, 1989).

The association of epilepsy and social deprivation is seen across all ages, although the association may weaken in adulthood as adults are less affected by social drifts (social deprivation causing epilepsy, which later result in much more deprivation) (Morgan et al., 2000). In one report the association was unrelated to downward social drift (Hesdorffer et al., 2005). The association between deprivation and seizure disorders in young children is determined mainly by material deprivation (Morgan et al., 2000).

The mechanisms underlying the association between epilepsy and poor socioeconomic position not fully understood (Heaney et al., 2002). But it is speculated that seizure disorders may be related to factors such as malnutrition, poor health and birth traumas, all of which are associated with socioeconomic position (Heaney et al., 2002; Morgan et al., 2000). Hesdorffer et al., also noted that low socioeconomic position is associated with many established risk factors for epilepsy such as cerebral vascular accidents, brain neoplasms, Alzheimer's disease and alcohol intoxication (Hesdorffer et al., 2005). Furthermore, social deprivation also make central nervous system more susceptible to conditions such as bacterial meningitis (Hesdorffer et al., 2005), which are associated with the development of seizure disorders including epilepsy. It is also postulated that the association between socioeconomic position and seizure disorders could be influenced by the vast psychiatric comorbidities and learning disabilities that are more common in people of lower socioeconomic position (Lorant et al., 2007). Furthermore, there may be a genetic predisposition to seizure disorders, but this is thought to be minimal, if any (Ottman et al., 1996).

### **2.3. Pregnancy and obstetric factors and seizure disorders**

Several studies have shown a significant association between obstetric complications and later development of seizure disorders. A Canadian-based population study identified several prenatal, and neonatal, factors associated with seizure disorders; those with the highest relative risks being eclampsia and early or neonatal seizures (Whitehead et al., 2006). In this study, small for gestation age contributed the greatest aetiology for epilepsy (7.4%) (Whitehead et al., 2006). This association may decrease over time since a study found that the incidence rate

ratios of seizure disorders in the first year of life were higher among children who were born with shorter gestational ages, low birthweight and intra-uterine growth retardation (Arnold et al., 1991; Sun et al., 2008b). In association studies, maternal complications such as toxemia and placental complications occurred more in mothers of children with epilepsy than in those of controls (Lilienfeld and Pasamanick, 1954). Another study also found a particular association between toxemia of pregnancy and epilepsy in children (Degen, 1978). The risk for seizure disorders in children with low birthweights can persist from childhood through to puberty (Sun et al., 2008a). Such case-control association studies however cannot establish a causal relationship between epilepsy and the risk factors investigated, unless such factors are prospectively studied in cohort or other prospective studies.

Obstetric factors may also be risk factors for other phenotypes of seizures disorders (Saliba et al., 2001), particularly those associated with cerebral palsy (Nelson and Ellenberg, 1984). This makes it difficult to understand whether such seizure disorders are due to the early life insults or result from the cerebral palsy related to such early pregnancy/obstetric complications. An earlier study by Ellenberg and Nelson found obstetric factors to be important in the development of cerebral palsy in children (Ellenberg and Nelson, 1979; Nelson and Ellenberg, 1984) and seizure disorders have been shown to be present in 15-55% of such children (Wallace, 2001). The risk for seizure disorders could be as high as 74% if learning disability is a comorbidity (Wallace, 2001), making the attribution of seizure disorders to early obstetric injuries complicated.

The mechanisms of developing seizures in circumstances of obstetric complications are still controversial. Although the pathological process for developing

seizure disorders following pre-eclampsia has never been clear, it has been suggested that pre-eclampsia in pregnant mothers causes an inflammatory process that can result in neonatal encephalopathy or localised cerebral ischaemia (Impey et al., 2001) which may later be associated with seizure disorders. In fact it has previously been proposed that a gradient of injury is possible with effects starting from early infancy extending through cerebral palsy, epilepsy and behaviour as a child grows older (Cannon et al., 2002) or the so called “continuum of reproductive casualty” (Pasamanick et al., 1956b). Prematurity can result in early neonatal seizures (Kohelet et al., 2004), which are then thought to increase the risk for later seizures by 22% in the first year and by 34% by two years (Garcias Da Silva et al., 2004). Pre-eclampsia increases the risk of later epilepsy in both term and pre-term babies, although the incidence rate was four times greater in the latter group (Wu et al., 2008). Prematurity modifies the association between pre-eclampsia and seizure disorders the same way cerebral palsy does (Wu et al., 2008). In fact, adjusting for cerebral palsy in one study rendered one significant association between small for gestational age and complex partial seizures insignificant (Rocca et al., 1987), but it is not clear if this would have been the case if all seizure types were studied. Other pregnancy and obstetric factors were not associated with complex partial seizures in the same study (Rocca et al., 1987).

### **2.3 Seizure disorders and behavioural problems**

Behavioural problems are common in children with seizure disorders such as epilepsy and they may occur in up to 50% of these children (Davies et al., 2003b). The prevalence of behavioural problems is often greater compared to population controls or those without epilepsy or a history of encephalopathy (Rutter et al.,

1970). There are new findings which indicate that behavioural problems may sometimes precede seizure disorders (Kanner, 2006), although this concept has been viewed with scepticism. A wide range of prevalence has been observed with studies reporting proportions ranging from 20% to 50% (Datta et al., 2005; Davies et al., 2003b; Rutter et al., 1970).

The risks for behavioural problems in children with seizure disorders have been widely studied with factors such as cognitive impairment, seizure frequency, and underlying neurological impairment being frequently mentioned (Datta et al., 2005; Keene et al., 2005; Rodenburg et al., 2005). The role of cognitive impairment in the development of behavioural problems in seizure disorders suggests that these problems may be associated with poor school attendance and performance in children (Aldenkamp, 2006; Aldenkamp and Bodde, 2005), and therefore educational interventions should be included in the comprehensive packages of care. It is however clear that there is considerable inconsistency in the risk factors mentioned, with only a few replications (Austin et al., 1992; Davies et al., 2003a). Further studies are therefore required to understand the cause of this variability of covariates of behavioural problems in epilepsy.

#### **2.4. Socioeconomic position and behavioural problems**

Studies have consistently demonstrated that lower socioeconomic position is associated with psychiatric morbidity, although the direction of causality remains controversial. While socioeconomic position predicts the development of mental health problems, specific psychiatric problems such as depression may result in downward changes in the socioeconomic position (Lorant et al., 2007). Two

important questions remain subjects of much debate. First, does low socioeconomic status predispose to behavioural problems? And secondly, do the existing behavioural problems cause a drift towards deprivation?

The causal pathway is not clear, although there is evidence to suggest that low socioeconomic position impacts directly the development of mental illnesses and indirectly through the factors indicative of financial capability—the so-called social causation and social selection hypotheses (Hudson, 2005). In another study, there was an improvement in some aspects of psychiatric disorders such as conduct and oppositional behaviour, but not anxiety and depressive disorders when the poverty index improved supporting a social causation explanation; but not a social selection (genetically predisposed) (Costello et al., 2003). Additionally, poverty seems to influence development of very pronounced behavioural problems particularly if associated with a history of epilepsy (Elliott et al., 2009). The association between low socioeconomic position and specific psychiatric problems such as anxiety is often limited because the diagnosis has been subject to several changes of terms and definitions over time (Muntaner et al., 2004).

To understand the mechanisms that cause behavioural problems in socioeconomically disadvantaged subjects, approaches such as ethnic stratifications, examination of migration, uncovering biological and psychological pathway involvement and multilevel mechanisms at different geographical aggregations have been proposed (Muntaner et al., 2004). These mechanisms are now providing new findings although the association between low socioeconomic position and behavioural problems had appeared well studied.

In addition to low socioeconomic position influencing the development of behavioural problems, there have been speculations that it may also determine treatment seeking patterns for people with mental illnesses. The outcome of treatment of psychiatric problems in deprived patients suggests that low socioeconomic position does not appear to influence the aspects of treatment for these behavioural problems but this could be influenced by other chronic comorbidities (Roy-Byrne et al., 2009). Low socioeconomic positions have been reported to be associated with shorter consultation times for treatment of mental illnesses, although this may have been a reflection of a lack of specialists in deprived areas (Videau et al., 2010). It may be possible that the relationship between low socioeconomic position and psychiatric problems is different in children since most of these studies above were based on adults.

## **2.5. Obstetric factors and behavioural problems**

The risk for behavioural problems such as hyperkinetic disorders is increased in children who are born preterm, those born at term with low birthweight (Linnet et al., 2006), and those born of mothers who smoked during pregnancy (Obel et al., 2010). Meta-analysis studies have indicated that both complications of pregnancy, abnormal foetal growth and development, and complications of delivery are associated with the development of schizophrenia, although the effect sizes are sometimes less than two (Cannon et al., 2002).

The effect of maternal smoking on the development of behavioural problems may be confounded by time-stable factors such as environmental and genetic factors just as has been the case in offspring criminality (D'Onofrio et al., 2010). One study

investigating the association between externalising problems and smoking during pregnancy found no association at all in children with conduct problems and oppositional defiant problems, but a very small association in those with ADHD (D'Onofrio et al., 2008). Additionally, the review of literature provides evidence that smoking during pregnancy is suspected to be associated with ADHD and ADHD-related symptoms (Linnet et al., 2003). In fact, studies show that smoking during pregnancy and when the child is five years old may be responsible for 25% and 16% of externalising or aggressive behaviours, respectively (Williams et al., 1998). Maternal smoking during pregnancy explained 4% of the variance of violence committed by adult male offenders and the risk for violent offences remains more than that in those whose mothers who did not smoke even when adjusted for biopsychosocial factors.

A group of children born preterm in Oxfordshire in the early 1990s demonstrated both educational (25%) and behavioural difficulties (19%) compared to the normal population (Huddy et al., 2001). In terms of specific behavioural problems, hyperactivity appears to be particularly associated with low birthweight (Marlow et al., 1989) and so are attention behavioural problems in children with a history of both low birthweight and prematurity (Aarnoudse-Moens et al., 2009; Guellec et al., 2011). There is relatively good concordance for attention and internalising behavioural problems in prematurity and low birthweight children rated by parents and teachers (Aarnoudse-Moens et al., 2009). Behavioural problems and low social competence associated by prematurity in older children are better explained by poor family stability and low intelligence quotient, respectively (Ross et al., 1990).

Low birthweight predicts hyperactivity in boys and peer problems in girls (Kelly et al., 2001). Records of children with behavioural problems showed more obstetric complications than controls and the spectrum of behaviours mostly affected children who were hyperactive, confused and disorganised (Pasamanick et al., 1956a). Various categories of low birthweight (low, very low and extremely low) have all predicted poorer cognitive outcomes in children (Aylward et al., 1989). Poor cognition and school performance in low birthweight children are associated with hyperactivity behaviour problems (McCormick et al., 1990). These associations are stronger with non-mechanical factors such as toxæmia compared to mechanical factors such as birth injuries due to prolonged labour or maternal pelvis inadequacy (Pasamanick et al., 1956a).

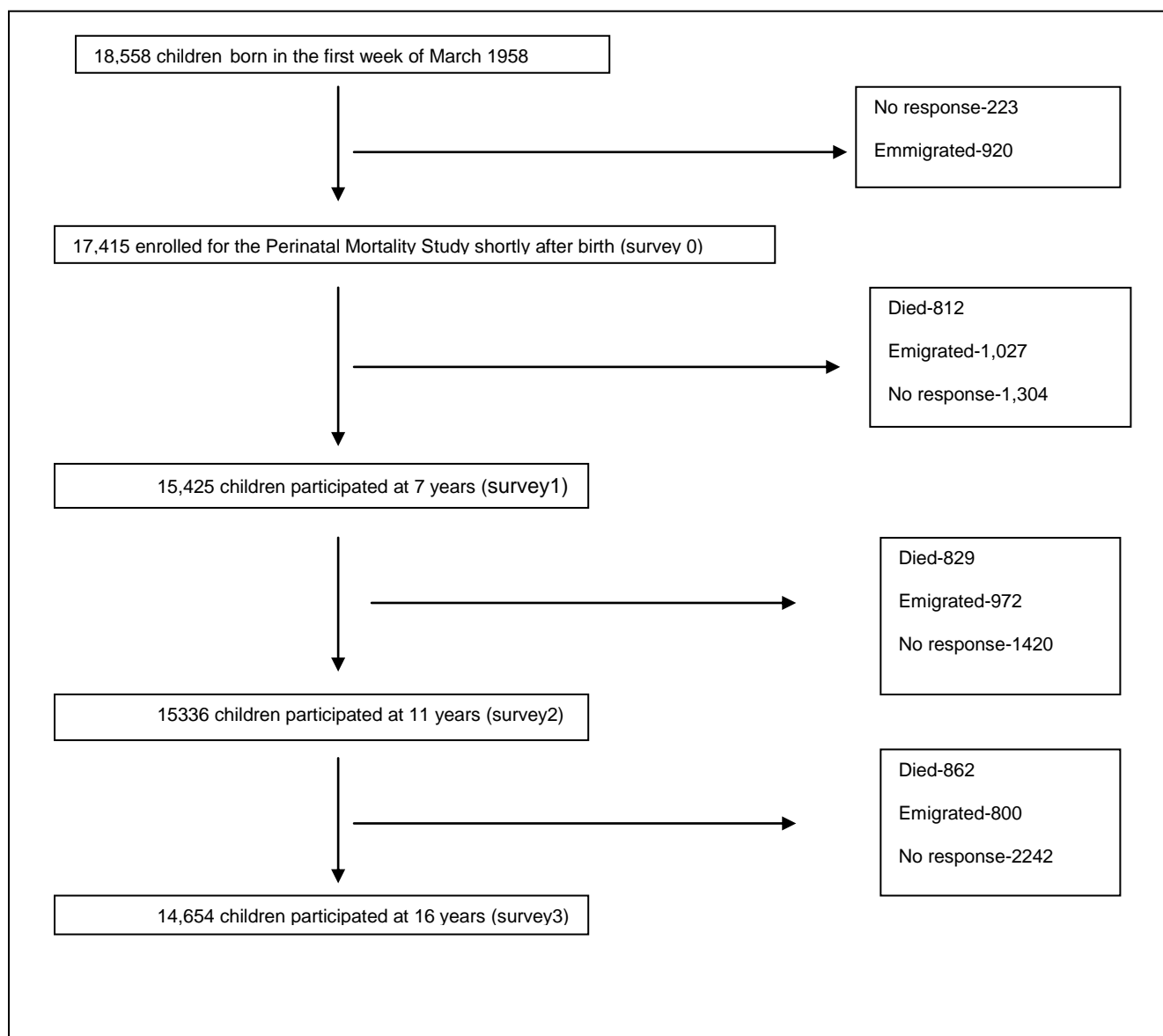
## **Chapter 3. Materials and Methods**

### **3.1. Study population**

The analysis was based on a cohort study of 17,416 who participated in the Perinatal Mortality Survey (PMS) out of a total 18,558 children born in England, Scotland and Wales in the first week of March 1958 (Grant, 1997). This is the sample for the National Child Development Study (NCDS). The analysis used information collected from parents and teachers at birth (survey 0), at 7 years of age (first survey), 11 years (second survey) and 16 years (third survey). The analysis focused on the first 16 years (surveys 0-3) because the focus was on the childhood determinants of epilepsy and behavioural disorders in children. Attrition was also less severe in these surveys. In fact, 83%, 83% and 79% of the original sample of 18,558 children participated at age 7 years, 11 years and 16 years, respectively (see

figure 1 below). Most of the information in the NCDS study was obtained from parents (who were interviewed by health visitors), head teachers and class teachers (who completed questionnaires), the schools health service (who carried out medical examinations) and the subjects themselves (who completed tests of ability and, latterly, questionnaires) (Power and Elliott, 2006).

**Figure 1. Derivation of study sample**



**3.2: Determination of seizure disorders**

A question about seizures or fits was asked at every survey of the NCDS study and the response given to that question forms the basis of the current analysis. Those who answered in the affirmative to this question were included in the analysis (see table 1 below). The positive responses that included faints, breath holding

attacks or hysterical attacks were excluded as it was not clear, without systematic validation, if these were syncopal, vagal or real seizure attacks (Benbadis and Allen Hauser, 2000). We attempted to include only afebrile seizures and therefore all febrile seizures were excluded. Because febrile seizures are very common in the first seven years of life (Mikati and Rahi, 2003), febrile seizures that occurred in the first survey (at age 7 years) were excluded using the updated data from previous analysis that had used the same dataset and who had their validated seizure or epilepsy data deposited back into the main dataset (Ross et al., 1980; Verity et al., 1985). In addition to performing an analysis on all seizure disorders, a sub-analysis was also performed on children with epilepsy (a history of two or more unprovoked seizures ) who had been confirmed to have had epilepsy from the first survey data reported in a previous study (Ross et al., 1980). Although there may have been studies on epilepsy published for the subsequent surveys, the data had not been uploaded or deposited in the central dataset by the time of this analysis (Richard F. Chin, personal communication), prompting us not to investigate epilepsy in the subsequent surveys. Consequently, in the second and third survey, we performed a sub-analysis of specific groups of children who had answered positively to a question on severe seizure disorders requiring the attention of a specialist in the first survey and of those who documented epilepsy as one of their handicaps to a question that sought to understand the types of handicaps that children may have had.

**Table 1. Determination of seizure disorders for the study**

Survey1: As deposited in NCDS database based on Ross et al analysis (Ross et al., 1980)		Survey2: Has the child ever had convulsions?		Survey 3: Has the child ever had any form of fit in which consciousness was lost, or any part of the body made abnormal movements (do not include emotional faints)?	
Seizure disorder	Number (15,425)	Seizure disorder	Number (15,336)	Seizure disorder	Number (14,654)
No seizures	14432	No seizures	12,334	No seizures	11,061
Probable seizures	178	Not applicable	2,473	Not applicable	3,117
Faints	220	Seizures after 7 years	384	Seizures	463
Hysterical attacks	80	Seizures after 7 years	33	Don't know	13
Definite epilepsy	59	Both before and after 7 years	44		
Possible epilepsy	6	Insufficient information on timing of seizures	68		
Probable febrile seizures	8				
Possible febrile seizures	23				
Seizures Undiagnosed as epilepsy	101				
Definite febrile seizures	213				
Breath holding attacks	86				
Blank spells	7				

All positive responses for afebrile seizure disorders were included in the final analysis. The analyses excluded all those children with febrile seizures, faints or hysterical attacks, breath holding attacks and blank spells.

### 3.3: Defining lower socioeconomic position

In this analysis the term socioeconomic position is preferred to socioeconomic status because the former refers to both social class (ownership and control over assets) and socioeconomic status (which measures mainly the levels of education or income) (Muntaner et al., 2004). Socioeconomic position was measured by three multi-dimensional constructs namely deprivation by social class, housing tenure and

financial difficult. Data on the first three constructs were collected shortly after the birth of the children, while that for the last one was available at 16 years. This analysis focuses on all three covariates, although there is evidence that all can be quantified or augmented through one question about tenure (Hauser, 1994).

Manual social class was a binary variable defined as 'manual': comprising social class III (Manual), Social Class IV and Social Class V, versus 'non-manual' comprising Social Classes I, II and III (Non-Manual). Housing tenure included rented accommodation (either council houses, privately rented houses or others undefined) versus owner occupied houses or all those with rent free housing. Financial difficulty was determined from a question about financial ability, which was asked in the first survey at 7 years, and the answer was dichotomised into a 'Yes' or 'No' response.

### **3.4. Pregnancy and obstetric complications**

The following obstetric complications were assessed: prematurity, pre-eclampsia, low birthweight and smoking during pregnancy. Prematurity was defined as delivery before 259 days. All newborns delivered on the 259<sup>th</sup> day or thereafter were considered mature (Henderson, 1945; Lou et al., 1992). Any newborn who weighed less than 2,500 grams (or 88.2 ounces) was considered low birthweight while babies weighing 2,500 grams (or 88.2 ounces) or more were considered of normal birthweight (Kramer, 1987). Pre-eclampsia was considered to have occurred if mothers experienced symptoms or signs of high blood pressure, all grades of toxæmia, proteinuria or received treatment for eclampsia (Roberts and Redman, 1993).

### 3.5. Defining of behavioural problems

Three categories of behavioural problems were investigated: total, internalising and externalising behavioural problems. Internalising and externalising behavioural problems were investigated based on an *a priori* assumption that the prevalence for these in children with seizure disorders would differ. Behavioural and emotional problems were assessed using the teacher-rated Bristol Social Adjustment Guides at age 7 and 11 years; and the teacher version of the Rutter scales at age 16 years (Elander and Rutter, 1996; McKenzie and Wilson, 1969). The Bristol Social Adjustment measures 12 symptoms. From these 12 measured symptoms, two scales namely internalising and externalising behavioural problems were formed. Internalising behavioural problems at 7 years were formed by summing the scores that measured unforthcomingness, withdrawal, depression, symptoms for internalising problems and nervous symptoms. Externalising behavioural problems at 7 years were the sum scores of anxiety, hostility towards adults, hostility towards children, writing off children and adults, anxiety for acceptance by other children kids, restlessness and inconsequential behaviour, as previously reported by Clark and colleagues (Clark et al., 2007).

The teacher-version of the Rutter scales at age 16 measured 18 items. Five of these items were: worries, solitary, miserable, fearful and fussy, which were summed to derive the internalising behavioural problem scale. Externalising behavioural problems at age 16 years were formed by summing reports of restlessness, fidgety, destructive, fights, not liked by others, irritable, twitches/mannerisms/tics, sucks thumbs, bites nails, disobedient, poor concentration, lies and bullies as previously reported by Clark and colleagues (Clark et al., 2007).

In both behavioural assessment tools used at the ages of 7, 11 and 16 years, behavioural problems were defined as those scores in the top 13%, moderate

behavioural problems as those in the top 50% but below 13%, while scores in the bottom 50% were deemed not to show behavioural problems (Ghodsian, 1983). A previous study on the same cohort had validated these two tools and showed that all the tools had both relatively good internal consistency and reliability in large populations (A Cronbach alpha of greater than 0.66 for internalising and externalising behavioural problems measured at all surveys using the two behavioural assessment tools) (Clark et al., 2007; Elander and Rutter, 1996).

### **3.6: Statistical analysis**

All analysis was performed using STATA (version 11; Stata corp, TX, USA). Measures of association were investigated using univariate and multivariate logistic regression analysis. Firstly, logistic regression was used to compare the distribution of factors of low socioeconomic positions and pregnancy or obstetric complications between (i) children who developed seizure disorders and those who did not, for each survey, and (ii) children who developed behavioural problems and those who did not for each survey. Secondly, logistic regression was used to compare the distribution of behavioural problems between children who developed seizure disorders and those who did not for each survey, adjusting for female sex and manual social class. The adjustment for these three variables was thought necessary since a previous important study identified sex and social material deprivation as important covariates of behavioural problems in children with epilepsy (Austin et al., 1992). The measures of associations consider all the prevalent cases i.e. all seizure disorders or new behavioural problems documented at that period or previous survey. Our assumption was that pathogenesis of seizures is a continuous

process in which seizures documented earlier may still have continued into the next survey under the possible effects of the early life factors being investigated. Ordinal logistic regression was employed for behavioural outcome measures because these were coded into three categories (definite, moderate and absence of behavioural problems). The analyses included incident cases of seizure disorders for each survey (i.e. those which had not been reported in the previous surveys) and prevalent cases of behavioural problems (rather than incident cases) for each survey since behavioural problems have been shown to have both a heterotypic and homotypic continuity across the growth period (Clark et al., 2007).

The hypotheses that a history of seizure disorders mediates the association between socioeconomic position or obstetric complications and behavioural problems was then tested by decomposing the total effects into direct and indirect effects using the logistic regression technique described previously in the background (Buis, 2010; Erikson et al., 2005). Because the mediation analysis requires seizure disorders to have occurred before the reported behavioural problems, we performed two mediation analysis: one for prevalent cases of behavioural problems documented at age 16 years using the status of incident seizure disorders at age 7 years, and another for the prevalence of behavioural problems by the 16 years using incident cases of seizure disorders documented at both age 7 years and age 11 years. The prevalent cases of behavioural problems by the age 16 years were preferred as a way to identify a large number of incident cases of seizure disorders (at age 7 years and 11 years combined), which would provide sufficient power to run further mediation analyses.

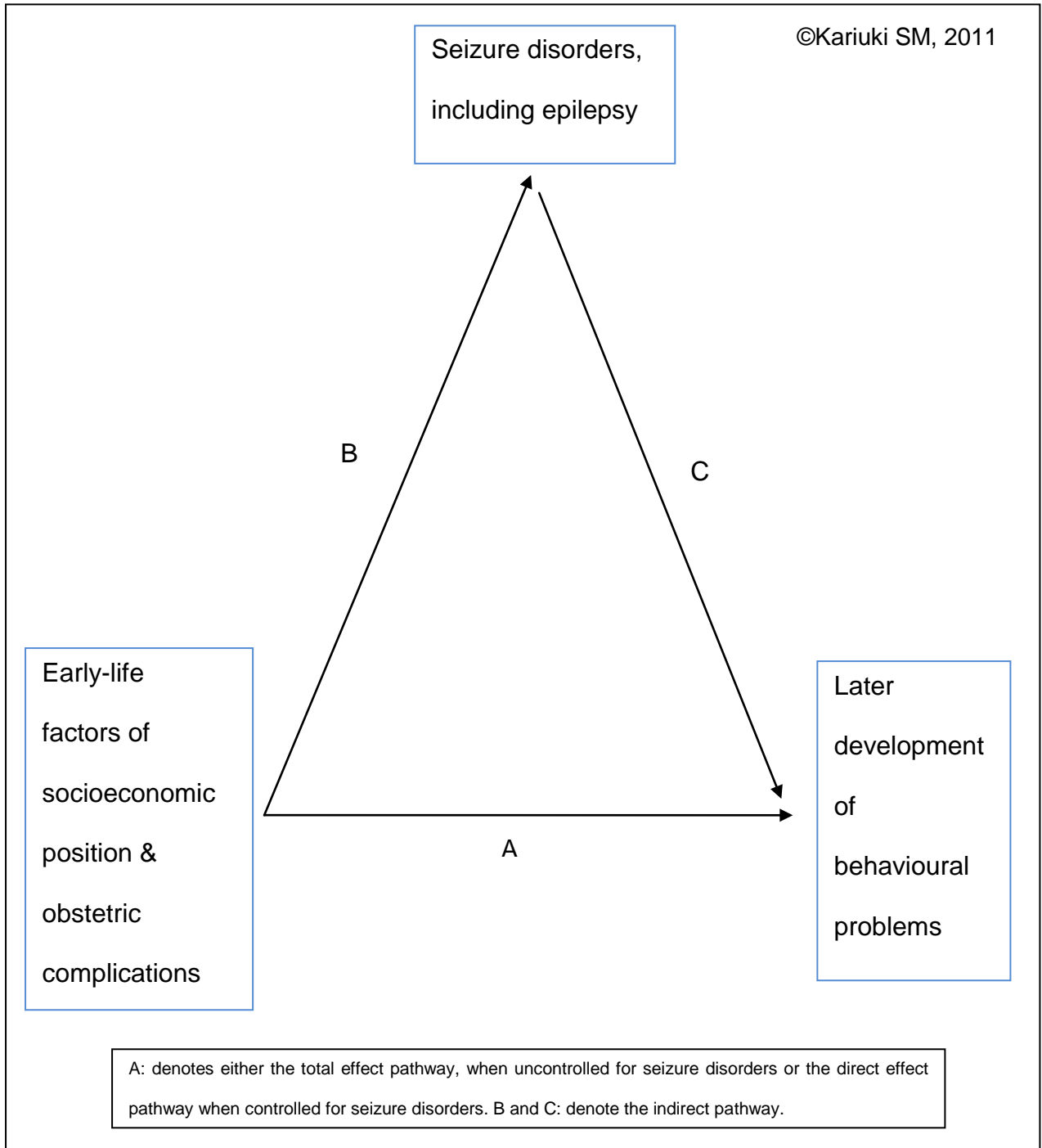
Total effect pathway was a measure of the likelihood that factors indicative of poor socioeconomic position or obstetric complications were associated with more

behavioural problems without controlling for the status of seizure disorders (see figure 2). The direct effect pathway referred to the measure of the likelihood that factors indicative of poor socioeconomic position or obstetric complications will increase the likelihood of developing behavioural problems even if the status of epilepsy is held constant. The indirect effect pathway is a measure of the likelihood that factors indicative of poor socioeconomic position or obstetric complications influence the development of seizure disorders in children in whom behavioural problems are common. This analysis can be accomplished in two ways: (1) Fix the logistic regression coefficients to be equal to the coefficients for the factors indicative of less affluent socioeconomic position and obstetric complications. Then compare the proportion with behavioural problems with a distribution of seizure disorders equal to the less affluent socioeconomic position or obstetric complications and the proportion with behavioural problems with a distribution of seizure disorders equal to the more affluent socioeconomic position or obstetric complications (Buis, 2010; Erikson et al., 2005); (2) Make the same comparison but fix the logistic regression coefficients to be equal to the coefficients of the more affluent socioeconomic position and obstetric complications (Buis, 2010; Erikson et al., 2005). The command *ldcomp* described by Erikson et al was used to compute the effects (Buis, 2010; Erikson et al., 2005). Three variables were entered into the model; the dependent variable as behavioural problems, direct or independent variable as the factors indicative of poor socioeconomic position or pregnancy/obstetric complications and indirect or mediating variable as the status of seizure disorders. Since the comparison of models that do not and those that do adjust for seizure disorders does not work well with non-linear models such as logistic regression, we included all variables of low socioeconomic position or

obstetric complications investigated in the association analysis above, although it is statistically recommended that only those that appeared significant in the above association analysis should be included in the mediation analysis (Buis, 2010; Erikson et al., 2005).

This method produces odds ratios (OR) for each effect pathway, their 95% confidence interval (95%CI), which are computed by bootstrapping the model with 50 permutations or replications, and the corresponding p-values (Buis, 2010). It also computes the proportion of the total effect mediated by seizures by dividing the logarithm of the OR for the indirect effect pathway over those of the total effect pathway (Buis, 2010). A p-value of  $\leq 0.05$  was considered significant for all statistical measures in this study.

**Figure 2: Direct effect, indirect effect and total effect pathways for the development of behavioural problems in children**



## **Chapter 4: Results**

### **4.1: General description**

Out of the 18,558 children born in the first week of March 1958, a total of 17,415 children had their data collected for the Perinatal Mortality Study. In the first survey of 1965, data was available for 15,425 children while in the second survey, conducted in 1969, data for 15,336 children was available. In the third survey of 1974, data for 14,654 children was available. The findings from only the children who responded or participated in each survey as described above are reported (see table 2).

The number and proportion of children from families with low socioeconomic position is shown in table 2. In the first survey, 10,371 children were living in families whose parents were in the manual social class and 681 children were being raised by single mothers. A total of 8,624 children were living in rented accommodation (council, private and/or others). Only 1,102 families reported having had financial difficulties when asked for their financial situation at age 16 years.

The number of pregnancy/obstetric factors investigated are summarised in table 2. The number of mothers who smoked during pregnancy was 5,783. The children who had been born premature were 2,773. A low birthweight was documented in 1,909 newborn children. Signs and symptoms of either pre-eclampsia or eclampsia were documented in 5,268 mothers.

The absolute number and the proportion of cases of children who were reported to have had a seizure disorder are in table 2. A total of 344 children were reported as having had a seizure in the first survey. In the same survey, epilepsy was confirmed in 69 children. In the second survey, 526 children had ever had a

seizure disorder, while 227 children had seen a specialist for treatment of what may have been a severe seizure disorder. In the third survey at 16 years, 476 children had a history of seizure disorders, with 14 reportedly having had a handicap in the epilepsy domain.

The number of children whose behavioural scores were in the upper 13<sup>th</sup> percentile was as follows. At age 7 years, total behavioural problems were seen in 4905 children, 5337 children had internalising behavioural problems and 5050 children had externalising behavioural problems. In the second survey (at 11 years) total behavioural problems were reported in 5044 children. At this time, internalising behavioural problems were seen in 5128 while externalising behavioural problems were seen in 5040. In the third survey (at 16 years) total behavioural problems were recorded in 8950. At 16 years, 7905 and 8548 children had internalising and externalising behavioural problems respectively.

**Table 2: The characteristics of children and the distribution of variables used in the study**

Characteristics	Perinatal Mortality Study at birth (n=17,415)	Survey 1 at 7 years (n=15,425)	Survey 2 at 11 years (n=15,336)	Survey 3 at 16 years (n=14,654)
Sex (female)	8411 (48.3%)	7508 (48.7%)	7450 (48.6%)	7107 (48.5%)
<b>Behavioural problems</b>				
Total behavioural problems	-	4905 (31.8%)	5044 (32.9%)	8950 (61.1%)
Internalising behavioural problems	-	5337 (34.6%)	5128 (33.5%)	7906 (54.0%)
Externalising behavioural problems	-	5550 (36.0%)	5040 (32.9%)	8548 (58.3%)
<b>Seizure disorders</b>				
All seizure disorders	-	344 (2.2%)	526 (3.4%)	476 (3.3%)
Epilepsy	-	69 (0.6%)	-	-
Severe seizures	-	-	227 (1.5%)	-
Reported epilepsy handicap	-	-	-	14 (0.01%)
<b>Socioeconomic position at birth</b>				
Manual social class	10,371 (59.6%)	-	-	-
House tenure	8,624 (49.5)	-	-	-
Single parent (mother)	681 (3.9%)	-	-	-
Financial difficulty	-	1,102 (7.1%)	-	-
<b>Obstetric or pregnancy complications</b>				
Pre-eclampsia during pregnancy	5,268 (30.3%)	-	-	-
Low birthweight at birth	1909 (10.9%)	-	-	-
Smoking during pregnancy	5,783 (33.2%)	-	-	-
Prematurity at birth	2,773 (15.9%)	-	-	-

**Most characteristics are missing either because the data for that survey were not used in this current analysis or the data were not available.**

#### **4.2: Socioeconomic position, pregnancy and obstetric factors and the risk for seizures disorders**

Several aspects of early life socioeconomic positions were significantly associated with the risk of developing seizure disorders, including epilepsy (see table 3). These included house tenure, which increased the risk for developing all seizure disorders by 1.26 times at age 7 years, 1.48 times at age 11 years and 1.32 times at age 16 years. Financial difficulty was associated with 2.11 times increased risk for epilepsy at age 7 years and 1.43 times increased risk for all seizure disorders at age 16 years. Social manual class, house tenure, and financial difficulty suggested an association for increased risk for all seizure disorders at 7 years and 11 years, severe seizures at age 11 years and all and severe seizure disorders

Among the factors of poor obstetric and pregnancy history, only pre-eclampsia and low birthweight appeared to be associated with increased risk for seizure disorders (see table 3). Pre-eclampsia increased the risk for all seizures at 11 years by 1.39 times and that for severe seizures at 11 years by 1.26 times. Low birthweight was associated with 1.66 times increased risk for all seizure disorders at 7 years, 2.27 times increased risk for epilepsy at 7 years, 1.35 times increased risk for all seizure disorders at 11 years, and 1.59 times increased risk for severe seizures at 11 years. The association between smoking during pregnancy and all seizure disorders at 11 years suggested an increased risk for although the evidence was weaker.

**Table 3: Socioeconomic position and obstetric and pregnancy complications and their associations with seizure disorders**

	Seizure disorders at 7 years		Seizure disorders at 11 years		Seizure disorders at 16 years	
Early life factors	All seizures (OR (95%CI), P-value)	Epilepsy (OR (95%CI), P-value)	All seizures (OR (95%CI), P-value)	Severe seizures (OR (95%CI), P-value)	All seizures (OR (95%CI), P-value)	Reported epilepsy handicap (OR (95%CI), P-value)
<b>Socioeconomic position</b>						
<b>Manual social class at birth</b>	1.32 (0.99-1.75), <b>p=0.051</b>	1.23 (0.63-2.31), p=0.525	1.22 (0.97-1.24), <b>p=0.082</b>	1.02 (0.73-1.43), p=0.900	1.11 (0.87-1.41), P=0.396	0.96 (0.27-3.85), P=0.958
<b>House tenure at birth</b>	1.26 (1.00-1.61), <b>p=0.044</b>	1.52 (0.90-2.55), p=0.118	1.48 (1.22-1.80), <b>P&lt;0.001</b>	1.28 (0.96-1.69), <b>P=0.092</b>	1.32 (1.09-1.62), <b>P=0.006</b>	0.86 (0.29-2.55), P=0.780
<b>Financial difficulty at 7 years</b>	1.59 (1.12-2.34), <b>P=0.008</b>	1.72 (0.82-3.62), <b>P=151</b>	1.78 (1.32-2.40), <b>P&lt;0.001</b>	1.47 (0.93-2.32), <b>P=0.097</b>	1.75 (1.29-2.38), <b>P&lt;0.001</b>	0.99 (0.13-7.71), P=0.997
<b>Single parent (mother)</b>	0.78 (0.41-1.47), P=0.435	0.83 (0.20-3.41), P=0.799	0.81 (0.46-1.42), P=0.458	1.14 (0.58-2.23), P=0.711	1.26 (0.85-1.97), P=0.315	-
<b>Obstetric and pregnancy complications</b>						
<b>Smoking during pregnancy</b>	1.10 (0.87-1.39), P=0.424	0.80 (0.45-1.40), P=0.433	1.21 (1.00-1.48), <b>P=0.053</b>	1.09 (0.82-1.46), P=0.553	1.13 (0.92-1.37), P=0.241	0.81 (0.25-2.58), P=0.720
<b>Pre-eclampsia during pregnancy</b>	0.87 (0.68-1.11), P=0.279	1.12 (0.65-1.93), P=0.684	1.18 (0.97-1.44), P=0.108	1.39 (1.04-1.85), <b>P=0.025</b>	1.26 (1.03-1.54), <b>P=0.022</b>	1.08 (0.36-3.23), P=0.889
<b>Low birthweight at birth</b>	1.66 (1.21-2.29), <b>P=0.002</b>	2.27 (1.17-4.35), <b>P=0.015</b>	1.35 (1.01-1.82), <b>P=0.045</b>	1.59 (1.05-2.42), <b>P=0.029</b>	1.24 (0.89-1.72), P=0.209	1.45 (0.30-6.94), P=0.643
<b>Prematurity at birth</b>	1.09 (0.81-1.46), P=0.573	1.34 (0.71-2.54), P=0.373	1.10 (0.85-1.44), P=0.451	1.14 (0.80-1.64), P=0.462	0.96 (0.74-1.24), P=0.740	0.60 (0.14-2.69), P=0.506

### **4.3: Seizure disorders and the risk for behavioural problems**

The behavioural outcomes in children with seizure disorders are shown in table 4. Most of the seizures disorders investigated at all the three surveys showed associations with behavioural problems across the various surveys.

For seizures disorders reported at seven years, the associations with the strongest evidence were seen for all seizure disorders at 7 years and the 1.63 times risk for total behavioural problems at 16 years, epilepsy and the 2.79 times risk for internalising behaviours at 11 years, epilepsy and the 4.68 times risk for total behavioural problems at 16 years, epilepsy and 3.40 times risk for internalising behavioural problems at 16 years and epilepsy and 2.62 times risk for externalising behavioural problems at 16 years.

Seizures disorders reported at 11 years with the strongest evidence for increased risk for behavioural problems were all seizure disorders and the 1.49 times increased risk for total behavioural problems at 16 years, all seizures disorders and the 1.44 times increased risk for internalising behavioural problems at 16 years, all seizure disorders and the 1.46 times increased risk for externalising behavioural problems at 16 years, severe seizure disorders and the 1.64 times increased risk for internalising behavioural problems at 11 years, severe seizure disorders and the 1.99 times increased risk for total behavioural problems at 16 years, severe disorders and the 1.64 times increased risk for internalising behavioural problems at 16 years and severe seizures and the 1.76 times increased risk for externalising behavioural problems at 16 years.

**Table 4: Adjusted behavioural outcomes in children with seizure disorders**

Seizure disorders	Behavioural problems								
	Total behavioural problems at 7 years (OR (95%CI)), P-value)	Internalising at 7 years (OR (95%CI), P-value)	Externalising at 7 years (OR (95%CI), P-value)	All behavioural problems at 11 years (OR (95%CI), P-value)	Internalising at 11 years (OR (95%CI), P-value)	Externalising at 11 years (OR (95%CI), P-value)	All behavioural problems at 16 years (OR (95%CI), P-value)	Internalising at 16 years (OR (95%CI), P-value)	Externalising at 16 years (OR (95%CI), P-value)
All seizures at 7 years (n=344)	1.27 (1.00-1.62), P=0.06	1.38 (1.08-1.76), P=0.01	2.6 (0.87-1.42), P=0.401	1.25 (0.96-1.61), P=0.097	1.38 (1.07-1.78), P=0.015	1.11 (0.86-1.44), P=0.421	1.63 (1.22-1.48), P=0.001	1.34 (1.01-1.77), P=0.040	1.38 (1.05-1.81), P=0.019
Epilepsy at 7 years (n=69)	2.11 (1.17-3.34), P=0.013	2.04 (1.15-3.62), P=0.015	2.16 (1.20-3.91), P=0.011	1.92 (1.05-3.51), P=0.033	2.79 (1.50-5.20), P=0.001	1.72 (0.95-3.12), P=0.072	4.68 (1.97-11.08), P<0.001	3.40 (1.58-7.33), P=0.002	2.62 (1.37-5.03), P=0.004
All seizures at 11 years				1.30 (1.10-1.60), P=0.012	1.30 (1.06-1.60), P=0.011	1.25 (1.00-1.53), P=0.037	1.49 (1.19-1.87), P<0.001	1.44 (1.19-1.80), P=0.001	1.46 (1.18-1.82), P=0.001
Severe seizures at 11 years				1.37 (1.01-1.90), P=0.044	1.64 (1.20-2.24), P=0.002	1.34 (0.98-1.84), P=0.066	1.99 (1.39-2.86), P<0.001	1.64 (1.16-2.32), P=0.005	1.76 (1.27-2.45), P=0.001
All seizures at 16 years							1.59 (1.27-2.00), P<0.001	1.38 (1.10-1.72), P=0.005	1.68 (1.34-1.12), P=0.452
Epilepsy handicaps at 16 years							1.23 (0.24-6.14), P=0.800	1.38 (1.10-1.72), P=0.005	1.67 (0.40-6.91), P=0.879

The behavioural outcomes for seizure disorders were determined for behavioural problems documented at that particular survey and for the subsequent surveys. Therefore, it is only seizures disorders documented at the first survey which would have allowed an association with behavioural problems for all surveys. The odds ratios are adjusted for female sex, a manual social class

#### **4.4. Socioeconomic, pregnancy or obstetric factors and the risk for behavioural problems**

All factors of low socioeconomic position investigated showed strong significant association with total or all behavioural problems, internalising behavioural problems and externalising behavioural problems (see table 5 below). Generally the odds ratio appeared to decrease with age i.e. they were much higher in the first survey (at age 7 years) compared with the second survey (at age 11 years) through to the third survey (at age 16 years), considering they are based on socioeconomic measures taken shortly after birth. Similarly, all the factors of poor obstetric and pregnancy history, except pre-eclampsia, were also associated with behavioural problems, through all the surveys. Pre-eclampsia was only significant for total behavioural problems at age 7 years, externalising behavioural problems at age 7 years, internalising behavioural problems at age 11 years and externalising behavioural problems at age 16 years.

**Table 5: Socioeconomic position and obstetric and pregnancy complications and their associations with behavioural problems in children**

	At 7 years			At 11 years			At 16 years		
Early life factors	All behavioural problems (OR (95%CI), P-value)	Internalising behavioural problems (OR (95%CI), P-value)	Externalising Behavioural problems (OR (95%CI), P-value)	All behavioural problems (OR (95%CI), P-value)	Internalising behavioural problems (OR (95%CI), P-value)	Externalising behavioural problems (OR (95%CI), P-value)	All behavioural problems (OR (95%CI), P-value)	Internalising behavioural problems (OR (95%CI), P-value)	Externalising behavioural problems (OR (95%CI), P-value)
<b>Socioeconomic position</b>									
<b>Manual social class at birth</b>	1.42 (1.32-1.52), P<0.001	1.31 (1.22-1.40), P<0.001	1.32 (1.23-1.41), P<0.001	1.49 (1.39-1.60), P<0.001	1.41 (1.32-1.52), P<0.001	1.42 (1.32-1.52), P<0.001	1.33 (1.24-1.43), P<0.001	1.10 (1.02-1.18), P=0.011	1.42 (1.32-1.52), P<0.001
<b>House tenure at birth</b>	1.48 (1.39-1.58), P<0.001	1.46 (1.37-1.55), P<0.001	1.35 (1.27-1.44), P<0.001	1.45 (1.36-1.55), P<0.001	1.34 (1.25-1.42), P<0.001	1.41 (1.33-1.51), P<0.001	1.29 (1.21-1.38), P<0.001	1.14 (1.07-1.22), P<0.001	1.40 (1.31-1.50), P<0.001
<b>Financial difficulty at 7 years</b>	2.22 (1.94-2.53), P<0.001	2.20 (1.93-2.50), P<0.001	1.93 (1.69-2.18), P<0.001	1.93 (1.72-2.15), P<0.001	1.98 (1.74-2.26), P<0.001	1.84 (1.64-2.11), P<0.001	1.69 (1.47-1.94), P<0.001	1.29 (1.16-1.45), P<0.001	1.76 (1.56-2.04), P<0.001
<b>Single parent (mother)</b>	1.41 (1.20-1.66), P<0.001	1.34 (1.15-1.57), P<0.001	1.47 (1.28-1.72), P<0.001	1.71 (1.45-2.01), P<0.001	1.49 (1.27-1.75), P<0.001	1.80 (1.53-2.11), P<0.001	1.82 (1.51-2.20), P<0.001	1.56 (1.32-1.85), P<0.001	2.17 (1.78-2.63), P<0.001
<b>Obstetric or pregnancy complications</b>									
<b>Smoking during pregnancy</b>	1.31 (1.22-1.39), P<0.001	1.23 (1.15-1.31), P<0.001	1.29 (1.21-1.38), P<0.001	1.22 (1.14-1.30), P<0.001	1.14 (1.07-1.22), P<0.001	1.24 (1.17-1.33), P<0.001	1.27 (1.19-1.36), P<0.001	1.16 (1.09-1.24), P<0.001	1.34 (1.25-1.44), P<0.001
<b>Pre-eclampsia</b>	0.92 (0.86-0.98), P=0.014	0.97 (0.91-1.04), P=0.433	0.90 (0.84-0.96), P=0.001	1.03 (0.97-1.10), P=0.331	1.08 (1.00-1.15), P=0.028	1.00 (0.93-1.07), P=0.943	0.94 (0.87-1.01), P=0.068	0.99 (0.93-1.06), P=0.790	0.92 (0.85-0.98), P<0.001
<b>Low birthweight</b>	1.86 (1.68-2.06),	1.81 (1.64-2.00),	1.80 (1.63-1.99),	1.52 (1.38-1.67),	1.68 (1.49-1.81),	1.53 (1.38-1.68),	1.58 (1.42-1.77),	1.63 (1.47-1.80),	1.50 (1.38-1.68),

	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
<b>Prematurity</b>	1.58 (1.45-1.72), P<0.001	1.59 (1.46-1.73), P<0.001	1.57 (1.44-1.70), P<0.001	1.66 (1.53-1.81), P<0.001	1.61 (1.48-1.75), P<0.001	1.64 (1.50-1.78), P<0.001	1.43 (1.30-1.56), P<0.001	1.35 (1.24-1.47), P<0.001	1.49 (1.36-1.63), P<0.001

The measures of association were between early-life factors of low socioeconomic position or pregnancy/obstetric complications and the prevalent cases of definite behavioural problems at each survey. The internalising and externalising behavioural problems had been determined based on an *a priori* assumption that there may be observed differences in the measures for these two categories of behavioural problems. Early life factors of socioeconomic position were taken shortly after birth, except financial difficulty which was taken at 16 years.

#### **4.5. Mediation (total effect pathway, direct effect pathway and indirect effect pathway) of behavioural problems**

There was strong evidence to suggest that most factors of low socioeconomic position and those of pregnancy complications favour the direct pathway of causation of behavioural problems (Table 6). This was consistently observed when mediation analysis was performed with behavioural problems at 16 years as the main outcome and seizure disorders at age 7 and 11 years, including epilepsy and severe seizure disorders for the same years, as the mediating variables. Children with parents reporting financial difficulties had an indirect effect on their behavioural problems at 16 years (with seizures at age 7 years and 11 years combined as mediators). Although this mediation was significant ( $p=0.015$ ), the proportion of total effect mediated was small (2.1%). The mediation analysis for behavioural problems in children whose mothers had reported having had pre-eclampsia was interesting in that the evidence for the direct pathway was relatively less compared to that for other factors of socioeconomic position or pregnancy and obstetric complications. In fact, exposure to pre-eclampsia with mediation of behavioural problems by severe seizures documented at 11 years showed a trend towards significance ( $p=0.047$ ) for the indirect pathway, and the proportion of total effect mediated estimated at 2.8%. The indirect effect of house tenure on behavioural problems mediated by all seizure disorders at 7 and 11 years and epilepsy at 7 years suggested support for indirect effect pathway, although evidence was weak. The proportion of total effect mediated by all seizure disorders for the development of behavioural problems in children who had been born underweight was high, but the strength of association was weak.

**Table 6: Mediation (total effects, direct effects and indirect effects) by seizure disorders of the association between socioeconomic or pregnancy factors and behavioural problems by age 16 years.**

Factors	Odds ratio for total effect pathway (95% CI)	P-value	Odds ratio for effect direct pathway (95% CI)	P-value	Odds ratio for indirect effect pathway (95% CI)	P-value	Proportion of total effect mediated by seizure disorders
<b>Mediation by all seizure disorders at age 7 years and 11 years</b>							
Manual social class at birth	1.433 (1.325-1.551)	<0.001	1.430 (1.322-1.547)	<0.001	1.003 (0.998-1.007)	0.336	<1.0%
House tenure at birth	1.329 (1.228-1.438)	<0.001	1.324 (1.226-1.430)	<0.001	1.004 (1.00-1.008)	<b>0.082</b>	1.3%
Smoking during pregnancy	1.320 (1.205-1.447)	<0.001	1.319 (1.204-1.445)	<0.0001	1.001 (0.997-1.005)	0.645	<1.0%
Single parent (mother)	1.497 (1.203-2.862)	<0.001	1.488 (1.199-2.845)	<0.001	1.006 (0.997-1.014)	0.203	1.3%
Financial difficulty at age 7 years	1.581 (1.384-1.805)	<b>&lt;0.001</b>	1.581 (1.384-1.805)	<b>&lt;0.001</b>	1.000 (0.997-1.002)	0.912	<0.1%
Prematurity	1.232 (1.12-1.365)	<0.001	1.233 (1.112-1.367)	<0.001	0.999 (0.993-1.005)	0.759	<1.0%
Pre-eclampsia	0.888 (0.814-0.970)	0.008	0.890 (0.816-1.970)	0.008	0.999 (0.995-1.002)	0.465	1.2%
Low birthweight	1.124 (0.979-1.301)	0.095	1.121 (0.975-1.297)	0.107	1.003 (0.998-1.009)	0.166	3.2%
<b>Mediation by epilepsy at 7 years</b>							

<b>Manual social class at birth</b>	1.434 (1.321-1.556)	<0.001	1.431 (1.318-1.554)	<0.001	1.002 (0.999-1.005)	0.268	<1.0%
<b>House tenure at birth</b>	1.329 (1.239-1.425)	<0.001	1.326 (1.236-1.422)	<0.001	1.002 (1.000-1.005)	<b>0.055</b>	<1.0%
<b>Smoking during pregnancy</b>	1.320 (1.224-1.424)	<0.001	1.322 (1.226-1.425)	<0.001	0.999 (0.996-1.002)	0.515	<1.0%
<b>Single parent (mother)</b>	1.497 (1.204-1.861)	<0.0001	1.500 (1.207-1.864)	<0.001	0.998 (0.992-1.004)	0.462	<1.0%
<b>Financial difficulty at 7 years</b>	1.611 (1.407-1.845)	<0.001	1.605 (1.402-1.838)	<0.001	1.004 (0.998-1.010)	0.237	<1.0%
<b>Prematurity</b>	1.232 (1.073-1.414)	0.003	1.229 (1.071-1.411)	0.003	1.002 (0.997-1.008)	0.453	<1.0%
<b>Pre-eclampsia</b>	0.888 (0.798-0.989)	0.030	0.887 (0.797-0.988)	0.029	1.001 (0.999-1.004)	0.411	<1.0%
<b>Low birthweight</b>	1.186 (1.063-1.324)	0.002	1.180 (1.056-1.319)	0.003	1.005 (0.998-1.012)	0.185	<b>3.0%</b>
<b>Mediation by severe seizures disorders at 11 years</b>							
<b>Manual social class at birth</b>	1.335136 (1.241-1.435)	<0.0001	1.335 (1.241-1.436)	<0.0001	0.999 (0.998-1.001)	0.850	<1.0%
<b>House tenure at birth</b>	1.287 (1.200-1.381)	<0.0001	1.286 (1.198-1.380)	<0.0001	1.001 (0.999-1.003)	0.239	<1.0%
<b>Smoking during pregnancy</b>	1.290 (1.188-1.399)	<0.0001	1.289 (1.1888-1.399)	<0.0001	1.000 (.999-1.001)	0.539	<1.0%
<b>Single parent</b>	1.874	<0.0001	1.873	<0.0001	1.000	0.619	<1.0%

<b>(mother)</b>	(1.561-2.250)		(1.560-2.248)		(0.998-1.002)		
<b>Financial difficulty at 7 years</b>	1.601 (1.423-1.800)	<0.0001	1.598 (1.421-1.796)	<0.0001	1.001 (0.998-1.004)	0.233	<1.0%
<b>Prematurity</b>	1.427 (1.279-1.593)	<0.0001	1.426 (1.278-1.592)	<0.0001	1.000 (0.998-1.002)	0.612	<1.0%%
<b>Pre-eclampsia</b>	0.885 (0.795-0.986)	0.026	0.882 (0.792-0.983)	0.023	1.003 (1.000-1.006)	<b>0.047</b>	<b>2.8%</b>
<b>Low birthweight</b>	1.129 (0.984-1.289)	0.083	1.124 (0.983-1.287)	0.088	1.004 (0.998-0.010)	0.193	<b>3.2%</b>

The direct effect pathway produces odds ratios without accounting for seizure disorders, direct effect pathway has the odds ratios accounted for seizure disorders. The odds ratios for the indirect effect pathway are a measure of the difference between total effect and direct effect pathway, and therefore should only be considered useful if there is statistical significance ( $p \leq 0.05$ ). The proportion of the total effect mediated was a measure of the logarithm of the odds ratio for indirect pathway divided by those of the total effect pathway. All odds ratios are reported to three decimal places to show the small differences between the total and indirect effects. Socioeconomic position was taken shortly after birth, except financial difficulty status which was taken at 16 years.



## **Chapter 5: Discussion**

### **5.1. Summary of main findings**

This is the first study to examine the development of behavioural problems in children following a history of seizure disorders taking into account the socioeconomic position and pregnancy or obstetric complications. The findings suggest that behavioural problems in children born into relative material disadvantage (lower socioeconomic position) or exposed to obstetric or pregnancy complications occur mainly through a direct pathway (independent of seizures), but a few children suggest that the casual pathway is through the indirect pathway (dependent of seizures). Almost all direct pathways for behavioural problems appeared strongly significant compared to only one indirect effect pathway (with pre-eclampsia as the exposure). These findings suggest that a different number of factors of lower socioeconomic position and pregnancy and obstetric complications may be associated with the development of both seizure disorders and behavioural problems in children.

### **5.2. Limitations and strengths of the study**

This analysis investigated seizure disorders in general and was only able to look at epilepsy in the first survey of the study. The additional analysis on children with severe seizures and reported epilepsy handicaps is based on small numbers, and therefore further larger studies are required to investigate the behavioural outcomes without any possible type one errors (Rothman, 2010). Although the occurrence of chance associations (type two errors) may have been possible, an analysis like this which is based on pragmatically developed hypotheses may help

reduce such errors (Rothman, 2010). The timing of assessments (i.e. if behavioural problems and seizure disorders were obtained at the same period or survey) may have been subject to reverse causality, which together with the recall bias could have led to regression dilution of measures of association (Frost and Thompson, 2000). It cannot be known if the children who did not participate in the study were possible cases of either behavioural problems or seizure disorders, which could have influenced the findings reported here. Because of lack of data, the effect of use of anti-epileptic drugs on behavioural outcomes was not investigated in the analyses, yet some studies have provided evidence that drugs such as phenobarbital and carbamazepine may be associated with severe behavioural disturbances (Banu et al., 2007), and these two drugs may have been in common use during the period of the study. Like any observational study, our analysis may have suffered from residual confounding because the measures obtained are not from a randomised study (Stram et al., 2002). The cohort used here may be thought by some to be outdated for applicability to more recent times as it involves the study of subjects who were children half a century ago.

The strength of this study derives from its cohort design which provides the ability to follow up the outcomes of early life exposures in children born in one week in Britain. Such a cohort is important in that the early life factors of socioeconomic position and pregnancy and obstetric complications are still prevalent now. The attrition rates were relatively low during this period of follow up and thus the power of the study is not as affected as would have been in subsequent follow-ups and the bias is therefore less. The data is from a national sample that is representative of all births in Britain and would allow extrapolation of these findings to the British population. The findings probably represent reliable summary of seizure disorders

since all febrile seizures were excluded and were systematically identified via validation of the clinical data from the general physicians during the first survey (at 7 years), a time before which febrile seizures are believed to be common (Mikati and Rahi, 2003). Epilepsy cases in the first survey had been pragmatically and accurately validated in a study reported in the early eighties by Ross *et al* (Ross *et al.*, 1980). An additional analysis was also performed on the effect of severe seizure disorders, either requiring the intervention of an epilepsy specialist in the second survey or reported by the parents as a 'handicap' in the third survey. One may speculate that the severe seizure disorders which require the child to see an epilepsy specialist or lead the parent to report the epilepsy as a handicap are possible candidates for a later diagnosis of epilepsy, although this would require rigorous follow up of patients or their hospital records to confirm this.

### **5.3. Socioeconomic position, pregnancy or pregnancy factors and seizure disorders**

It appears from this analysis that socioeconomic deprivation may be more important than pregnancy factors in the development of seizure disorders in the children studied. All factors of socioeconomic position, except for single marital status of the mother, predicted the risk of seizure disorders at several points across the surveys. In terms of pregnancy history, only low birthweight and pre-eclampsia were associated with seizures at the first and second surveys. Our findings are in keeping with previous work that has supported a predisposition for seizures in children living in poverty (Heaney *et al.*, 2002). It is thought that poverty may negatively determine the health seeking behaviours of patients, and thus increase a propensity for seizures in these patients (Hesdorffer *et al.*, 2005). The risk for seizures may be enhanced if the disadvantaged children also have a genetic

propensity for seizures (Baulac et al., 2004). It is plausible that pre-eclampsia could be associated with later development of seizures because a pro-inflammatory mechanisms has been previously suggested, which could culminate in increased rates of seizures (Impey et al., 2001). Although exposure to obstetric or pregnancy risk factors were not particularly associated with seizure disorders in this analysis compared to socioeconomic position, this should not be construed to mean that they are not important risk factors for seizures. These factors have been shown to be important in early neonatal seizures and it is possible that their effects may have reduced by the time seizures began to be assessed at age 7 years. Future studies could investigate if obstetric factors are important in early life seizures including febrile seizures, which occur as early as the first two months of life.

#### **5.4. Seizure disorders and behavioural problems**

Seizure disorders showed an association with behavioural problems at several points across the surveys. The associations are more likely to be representative of the behavioural outcomes because of the adjustment of potential confounders such as female sex and relative material deprivation, both which have been reported as important correlates of behavioural problems in children with seizure disorders especially epilepsy (Austin et al., 1992). What is clear is this association was more common with epilepsy and severe seizure disorders, suggesting that the effect may increase with factors indicative of severe seizure disorder (Austin et al., 1992). For epilepsy documented at 7 years, an association with behavioural problems was more evident in the third survey, suggesting a process of ongoing pathogenesis in the brain. Previous studies have observed that behavioural problems could be due to an underlying neurological problem and the

plastic effect of seizure activity in the brain, which would obviously take some time to develop (Austin et al., 2002).

Since there was a strong association between all seizure disorders together and behavioural problems, these findings support the view that the psychopathology of seizures such as acute symptomatic seizures or even non-recurrent seizures should not be overlooked as they may be clinically important. There is indeed evidence that acute symptomatic seizures or even febrile seizures (often considered benign) could also have a behavioural or intellectual disadvantage (Idro et al., 2007; Verity et al., 1998). This should however be investigated with cohort data by specifically following children with such seizures over time for behavioural outcomes. Syndrome-specific behavioural outcomes using cohort studies is thus recommended, where possible.

Despite the growing literature in this field, there is still a lack of data on behavioural outcomes in epilepsy in resource poor settings such as sub-Saharan Africa. We have demonstrated that half of older children in rural Kenya have reported severe behavioural problems, and these problems are associated with cognitive impairments and seizure frequency (Manuscript submitted to *Epilepsy and Behavior*). This lack of data in developing countries therefore hampers the applicability of findings from the developed world to a population to a region often composed of children who are more vulnerable. This vulnerability is enhanced by the high incidence of infectious diseases such as falciparum malaria, which may also modify the encephalopathy that leads to the development of behavioural problems (Idro et al., 2010; Kariuki et al., 2011). Furthermore the first line anti-epileptic drugs used in these resource-limited countries include phenobarbital, which may be

associated with specific behavioural problems such as hyperactivity (Banu et al., 2007).

### **5.5. Socioeconomic position, pregnancy or pregnancy factors and behavioural problems**

The findings from this study are consistent with studies that have suggested lower socioeconomic position and obstetric complications are important in the development of behavioural problems (Costello et al., 2003). This association has been investigated by most studies and suggests that a causal relationship exists (Costello et al., 2003; Lorant et al., 2007; Muntaner et al., 2004), although some of these are based on adult data. It is not clear how low socioeconomic position causes behavioural problems but two theories have been postulated, social causation and social selection (Costello et al., 2003; Muntaner et al., 2004). It is likely that the association we see in our analysis represents both the social causation and the social selection causes of behavioural problems since our study population was composed of children, whose behavioural problems can result from or lead to deprivation, which later can increase susceptibility to more behavioural problems (downward social drift) (Birbeck et al., 2007). It can be speculated that alleviation of poverty or improvement in living standard would likely result in a simultaneous decline in the prevalence of behavioural problems in children.

### **5.6. Mediation analysis for behavioural problems**

There was strong evidence in support of direct effects of early life factors on the development of behavioural problems as explained or mediated by seizure disorders. The indirect effect pathways for development of behavioural problems as

explained or mediated by seizures in children with pre-eclampsia was significant. The proportion of total effect of low birthweight on behavioural problems was relatively big, although the evidence was weak. Since pre-eclampsia and low birthweight were the only factors of pregnancy or obstetric complications that favoured an indirect pathway for development of behavioural problems could mean that there is a biological relationship between pre-eclampsia or low birthweight and later development of seizure disorders. This is convincing considering that the literature has suggested an inflammatory process in pre-eclamptic mothers which can injure the unborn child's brain increasing the later development of seizures (Impey et al., 2001). Additionally, this suggests the question whether the relation between pre-eclampsia and seizures has a genetic predisposition as this could be used as a basis for future genetic studies of the risk of seizures in which genetic distribution is compared between children born of pre-eclamptic mothers and those of mothers who did not get pre-eclampsia. Similarly, low birthweight is thought to increase neurological sequelae in those genetically predisposed (Rice et al., 2006) and it may be possible that low birthweight plays a role in genetic shape-up early on in life, which if so, would suggest it has a biological contribution to neurological sequelae.

That most behavioural problems developed through the direct effect pathway compared to indirect effect pathway is important. This supports the hypothesis that appropriate child and maternal health care and alleviation of poverty may significantly reduce behavioural problems in a proportion of children. Since behavioural problems often lead to serious psychiatric problems in what has often been called a heterotypic or homotypic continuity (Clark et al., 2007; Gillberg et al., 1986), their prevention is both cost-effective and will improve the quality of life for

these children. Considering that previous studies have already begun to show a decreased lack of supply of general physicians for the management of mild mental health problems (Videau et al., 2010), this study calls for increased or sustained deployment of general physicians to deprived regions to help identify behavioural problems so that cases can be appropriately referred for specialised management. The control of behavioural problems in children disadvantaged by poor socioeconomic positions and factors of obstetric or pregnancy complications is more feasible through the direct pathway especially in relatively deprived areas of Britain, as opposed to through the indirect pathway that would require the intervention of epilepsy specialists who are often few in such regions. It should however be emphasised that indirect effect pathways examined in these models are relative to seizures and it may be likely that other chronic illnesses other than seizures (not investigated here) could have a greater mediating effect that would result in a diminished direct effect pathway in the same children studied.

These findings are intriguing in that although there is prior strong evidence of an association between seizure disorders and behavioural problems, most behavioural problems in children disadvantaged by early life deprivation and pregnancy complications do not occur through the seizure pathway. This result needs careful interpretation. First it could mean that the development of behavioural problems in children with seizures is either related to the disruption caused by the seizures themselves or an underlying neurological disorder and is not in any way influenced by prior poor socioeconomic position or obstetric complications that might have contributed to the development of seizures (Austin et al., 2002). Secondly, the finding could suggest that seizures are not important mediators for behavioural problems in children exposed to the aforementioned factors, but possibly to those

children exposed to other risk factors for both epilepsy and behavioural problems not investigated in this analysis. Such possible factors which should be investigated in future studies to confirm a possible mediation by seizures when they cause behavioural problems include early life or previous hospitalisation with central nervous system infections such as bacterial meningitis and a history of hypoxic ischemic encephalopathy, which could have been caused by birth-related insults. The effect of bacterial meningitis and hypoxic-ischaemic encephalopathy on behavioural problems as explained or mediated by seizures should be studied because both seizures and behavioural problems could result from these factors (Finer et al., 1983; Pikis et al., 1996).

### **5.7. Conclusions**

The findings from this study confirms those of previous studies that found an association between lower socioeconomic position and pregnancy or obstetric complications and the increased risk for developing both seizures disorders and behavioural problems. However, the association between these early life factors and the development of behavioural problems is not particularly mediated by seizure disorders. Although it appears that lower socioeconomic position may be more important than pregnancy or obstetric complications in predisposing toward seizures in the children studied, it is likely that the pregnancy or obstetric complications may prove crucial in predisposing toward causing early life seizures such as neonatal seizures or febrile convulsions, which we did not investigate in this analysis.

The findings from this study support the need for increased health services for epilepsy and behavioural problems in deprived regions of even developed countries. In particular improved maternal and child care or specific epilepsy care may be very

useful in combating psychological and seizure disorders in children. Further analyses are needed to investigate how seizure disorders mediate the development of behavioural and/or psychiatric problems in children who have previously had central nervous infections which are important problems in some parts of the world.

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## **Appendix**

The voluminous study protocols, guides and questionnaires used for this and other NSDS analyses can be found in the website below:

<http://www.cls.ioe.ac.uk/studies.asp?section=000100020003>