What have birth cohort studies asked about genetic, pre- and peri-natal exposures and child and adolescent onset mental health outcomes? A systematic review.

Short title: Systematic review of birth cohort studies

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Abstract

Background: Increased understanding of early neurobehavioural development is needed to prevent, identify and treat childhood psychopathology most effectively at the earliest possible stage. Prospective birth cohorts can elucidate the association of genes, environment and their interactions with neurobehavioural development.

Methods: We conducted a systematic review of the birth cohort literature. On the basis of internet searches and 6,248 peer-reviewed references, 105 longitudinal epidemiological studies were identified. Twenty studies met inclusion criteria (prospectively recruited, population-based cohort studies including at least one assessment before the end of the perinatal period and at least one assessment of behaviour, temperament/personality, neuropsychiatric or psychiatric status before age 19 years) and their methodologies were reviewed in full.

Results: While the birth cohort studies did study some aspects of behaviour and neurodevelopment, observations in the early months and years were rare. Furthermore, aspects of sampling method, sample size, data collection, design and breadth and depth of measurement in some studies made research questions about neurodevelopment difficult to answer. Existing birth cohort studies have yielded limited information on how pre- and peri-natal factors and early neurodevelopment relate to child psychopathology.

Conclusions: Further epidemiological research is required with a specific focus on early neurodevelopment. Studies are needed which include measures of early childhood psychopathology and involve long term follow up.

Keywords: Epidemiology, Child Development, Longitudinal Studies, Mental Health, Perinatal

Abbreviations: ADHD: Attention deficit hyperactivity disorder; ASC: Autism Spectrum Conditions; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

Introduction

A sound understanding of normal and abnormal behavioural and neurological development in the early years of life is necessary before we can prevent, identify and treat early onset neurodevelopmental and mental health problems. We lack a detailed knowledge of the aetiology, risk factors, correlates, onset, early symptoms, course and prevalence of child psychiatric conditions including conduct disorder (CD) (Moffitt et al., 2008), oppositional defiant disorder (ODD) (Karnik, McMullin, & Steiner, 2006), tic disorders, bipolar disorder, attention-deficit hyperactivity disorder (ADHD) (Stefanotis & Baron, 2007) schizophrenia (Read, van Os, Morrison, & Ross, 2005) and autism spectrum conditions (ASC) (Rapin & Tuchman, 2008). Some of these conditions will be discussed in more detail to provide specific examples of the issues that need to be addressed. ODD and CD, although not strictly neurodevelopmental disorders, are both very strongly comorbid with ADHD. Many studies that have reported outcomes in terms of ODD and CD have not included data on how many of the cases included actually did have comorbid ADHD. Therefore, in order to cover ADHD as thoroughly as possible, literature discussing ODD and CD outcomes have been included in the present review.

Risk Factors and Correlates

The literature on CD provides a useful example of the gaps in our knowledge of risk factors of neurodevelopmental disorders. Many risk factors and correlates have been proposed but few have been established as causative (Earls & Mezzacappa, 2005; Moffitt et al., 2008). For example, harsh and inconsistent parenting has been repeatedly shown to be associated with CD/ODD, but we do not know to what extent it is a cause or a consequence (Frick, 2006). Perinatal complications, genetic predisposition, neurocognitive deficits, low IQ and parental antisocial behaviour are also implicated, but many outstanding questions remain about the

exact nature of these risk factors and the way in which they may interact (Moffitt et al., 2008). Epidemiological studies of CD/ODD in preschool children in the general population are rare (Kadesjö, Hagglof, Kadesjo, & Gillberg, 2003; Kim-Cohen et al., 2005; Egger & Angold, 2006). Furthermore important nosological questions remain, for example the contribution of callous-unemotional symptoms, the importance of gender differences, and the relationship between ODD, CD and anti-social personality disorder (Moffitt et al., 2008). We also need to know more about the key genetic determinants and the utility of physiological biomarkers.

Autism research provides another useful illustration: we know that genetic factors are very important in autism, (Veenstra-Vander, Christian, & Cook, 2004) and siblings are at much increased risk of being diagnosed with ASC after infancy, (Zwaigenbaum et al., 2005a), but again methodological issues preclude generalisable conclusions as to the magnitude of the risk involved. Longitudinal population-based studies are required to establish the utility of these markers and consequently to develop robust early screening and diagnostic tools.

Course and Stability of Disorders

Continuing with the example of autism, while several studies have assessed prevalence (Gillberg & Wing, 1999; Fombonne, 1999; Yeargin-Allsopp, Rice, Karapurkar, & et al., 2003; Baird et al., 2006; Posserud, Lundervold, & Gillberg, 2006; Williams, Higgins, & Brayne, 2006) there is less conclusive evidence about the course and stability of the disorder, especially throughout the first five years of life. There is a significant body of evidence that predictors of autism exist in early childhood (Dahlgren & Gillberg, 1989; Gillberg et al., 1990; Zwaigenbaum, Bryson, Rogers, & et al., 2005b; Yirmiya & Ozonoff, 2007). These include failure to react to own name, decreased initiation of joint attention, odd reactions to

sensory stimuli, and pathological or unusual motor/movement patterns. However, referral and recall bias, small sample size and other methodological considerations still limit the general predictive and clinical value of such parameters.

Problems with existing studies of early neurodevelopment and child psychopathology

Many studies that focus on the early determinants of child psychopathology are weakened by their methodology. Clinical samples cannot give a comprehensive understanding of overlap with normality and issues of co-morbidity as the thresholds of discrete conditions are already defined, while cross-sectional studies cannot enhance our understanding of developmental processes. As Pickles and Angold (2003) state, in order to understand the relationships between psychopathology, its aetiology, outcome and other factors, "we need to adopt a truly empirical approach that is unblinkered by either categorical or dimensional prejudices" (p548). Retrospective studies of early predictors of psychopathology are limited by issues of recall bias while prospective cohorts of subjects at 'high risk'(Besag, 2006; Cassell et al., 2007; Gamliel, Yirmiya, & Sigman, 2007; Iverson & Wozniak, 2007; Landa, Garrett-Mayer, Landa, & Garrett-Mayer, 2006; Loh et al., 2007; Merin, Young, Ozonoff, & Rogers, 2007; Toth, Dawson, Meltzoff, Greenson, & Fein, 2007; Yirmiya et al., 2006; Zwaigenbaum et al., 2005b; Yirmiya et al., 2007; Zwaigenbaum et al., 2005a; Zwaigenbaum et al., 2005a) may reveal early indicators of neurodevelopmental disorders, such as autism, but are subject to a variety of forms of selection and ascertainment bias. For example, prospective studies of children exposed to smoking in pregnancy and of children with very low birth weights have shown increased rates of ADHD and of ADHD/autism symptoms (Hultman et al., 2007; Indredavik, Brubakk, Romundstad, & Vik, 2007), but to what extent such factors alone can contribute to these difficulties can best be determined in the context of general population

birth cohort studies. Furthermore, approaches limited to 'high risk' families will inevitably fail to help us understand the common sporadic cases.

Early intervention in disorders of social development is, *a priori*, more likely to be effective than late intervention, but data confirming this assertion are lacking largely because of the lack of sensitive and specific techniques to identify at-risk children. In order to develop complex interventions to improve health (Campbell et al., 2000), there is a need to define the causal models for these disorders better, which in turn require epidemiological investigations (Hardeman et al., 2005; Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005). Large population studies have been extremely rare in this field.

Advantages of the birth cohort methodology

Prospective, unselected birth cohorts, followed from pregnancy or birth, allow us to study early neurodevelopment and behaviour without the methodological weaknesses outlined above. If a representative sample of the general population can be recruited in the pre- or perinatal period and retained throughout childhood, difficulties with selection bias can be overcome. Early exposures, which can be considered in understanding the development of childhood psychopathology, include those present at the time of conception (genetics), during pregnancy (the intrauterine environment: toxins, placental function, maternal cortisol etc), at birth (asphyxia, trauma etc) and during the postnatal period (infection, feeding modality, parent-infant interaction etc). Relationships between exposures, outcomes and other influential factors can be considered in a temporal context to allow mapping of developmental trajectories, and overlap between disorders and between psychopathology and normality can be elucidated (Shulruf, Morton, Goodyear-Smith, O'Loughlin, & Dixon, 2007).

Although selection bias is less of an issue for birth cohorts, this design always carries the risk of differential attrition over time, giving a less stable basis to the generalisability of findings.

Advantages of the ante-natal birth cohort methodology

The advantages of a birth cohort methodology are capitalised upon if recruitment takes place antenatally. In a recent review paper, Shulruf et al (Shulruf et al., 2007) highlight the importance of taking an holistic view of child development in order truly to understand "the complex way in which developmental trajectories across different domains are determined and interrelated" (p208). Shaw et al (Shaw et al., 2006) demonstrated this by finding that the *trajectory of change* in the thickness of the cerebral cortex is most closely related to level of intelligence rather than cortical thickness itself, measured at any one point in time. Any developmental outcome can only be considered as a snapshot of any one trajectory, and as such it is essential to ensure that we measure a range of relevant factors longitudinally from as early as possible. There are clear advantages in measuring such factors as parental personality/mental health and family functioning before the arrival of a baby, as the baby may influence these, and Shulruf et al (Shulruf et al., 2007) conclude that any new longitudinal study of child development should gather data in the antenatal period.

We conducted this review with a view to identifying systematically which birth cohort studies measured important exposures in the pre- and/or peri-natal period and also measured behaviour, temperament/personality, parent-child relationships, language and social functioning, neurodevelopment, intellectual functioning and psychopathology, including autism, in childhood.

Methods

Birth cohort studies (published and in progress) were identified from 6,248 references retrieved from the following internet-based bibliographic databases to May 2006: 1. EBM Reviews, 2. British Nursing Index, 3. CINAHL, 4. EMBASE, 5. ERIC, 6. OVID Medline, 7. PsychINFO. The search term 'birth cohort' was used. Secondary referencing, birth cohort study websites, internet search engines and consultation with workers in the field identified further studies. Further searches using these methods were employed to gather as comprehensive information as possible on identified studies to the end of 2007, and information was also requested directly from 21 birth cohort study research teams (see Table 14 - online).

Inclusion criteria

The following inclusion criteria were used:

1. Human study population;
2. Birth cohort study defined by:
    a) Identification antenatally or at birth;
    b) Cohort recruited from an unselected population (rather than clinical) base;
    c) Some prospective data collection from antenatal/perinatal period;
    d) Measures to include at least one assessment of behaviour, temperament/personality, neurodevelopmental or psychiatric status (questionnaire or direct observation) before age 19 years.

In total, 105 birth cohort, epidemiological or longitudinal studies were identified of which 20 studies met the inclusion/exclusion criteria and were reviewed in full (Tables 1-4). Details of studies that did not meet the criteria are presented in Table 13 (online). A fuller account of the measures of the included studies can be found in Tables 5-12 (online). We discuss issues

of study design and measurement for the 20 included studies, and give a brief outline of certain seminal studies that did not fully meet the criteria.

Results

Basic details of each of the 20 included studies are outlined in Table 1, with further summarised information given in Tables 2 to 4 (online). Twelve studies referred to cohorts recruited antenatally and the remaining eight cohorts enrolled around the time of birth. The sample sizes of the studies ranged from 831 to 100,000 and recruitment rates from approximately 30% to 99% of those targeted. Only three studies (Christchurch, Copenhagen County, and the Norwegian Mother and Child Cohort) focussed specifically on autism / child mental health / neurodevelopment and the sample sizes of these studies ranged from 1,265 to 88,027. Only two of these studies (Christchurch and Copenhagen County) had measures of neurodevelopment in the first two years in the *whole cohort*, but the relatively small sample size in one of these (Christchurch) precluded study of rarer disorders, and Copenhagen County did not recruit antenatally, precluding a full understanding of the pre-natal environment.

Table 1 here

We now present information on sampling and methodology for each of the 20 studies meeting inclusion criteria, starting with the 12 antenatally derived cohorts, followed by the eight cohorts recruited at birth. We then describe five key excluded studies. Within these subsections the studies have been ordered alphabetically.

Cohorts recruited antenatally

Amsterdam Born Children and their Development: 2003-2005,(http://www.abcd-study.nl/). Focusing, in part, on psychosocial health, this current study from the Netherlands follows

7,051 infants from pregnancy through to 5 years of age (van der Wal & et al, 2006). A range of demographic, biological, psychosocial and behavioural information on the parents was collected antenatally, with routine birth data recorded at 4-7 days. Information on the post-natal environment, including mother's behaviour and psycho-social status, was collected at 3 months. No data collection occurred between 3 months and 5 years. While infant crying and maternal soothing and mother-child relationship was assessed there was no assessment of infant language or psychopathology. Measures of child cognitive development and psychological wellbeing are planned for the next data collection phase at age 5 years.

Avon Longitudinal Study of Parents and Children: 1990-1992

(http://www.bristol.ac.uk/alspac/protocol). This study from the Bristol area in the UK included broad examination of biological, environmental, social, psychological and psychosocial exposures and their various health and developmental outcomes in around 14,000 mother-child dyads (Golding, Pembrey, Jones, & the ALSPAC Study Team, 2001). Enrolment is estimated at between 80% and 90% of all pregnancies in the defined target area, and overall retention is reasonable. Data collection starts from pregnancy and is frequent until 5 years of age, with ongoing regular data collection involving children and parents. The children are now 17-18 years old. A range of demographic, biological, psychosocial and behavioural information on both the mother and her partner was collected antenatally. DNA samples have been obtained for approximately 10,000 mothers, 10,000 children and 800 fathers (P3G Observatory, 2007). Routine birth data are recorded, and postnatal environment assessed at 4 weeks. Behaviour, language, communication and neurodevelopment are assessed at a range of points throughout childhood. Mother-child interaction was however only assessed in the 'Children in Focus' sub-sample of 1000 randomly selected children, although questions on parent-child conflict and relationship were included in the 78 month

questionnaire to parents. Child psychopathology was measured in the whole cohort using the Development and Well-Being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) at 91 months; at 11 years children were assessed for borderline personality disorder; and at 13 years questionnaires to children included items on eating disorders. Depression (13 and 14 years), psychosis (13 years) and theory of mind (14 years) were also assessed in clinic visits, but attendance was fairly low so the findings may not be representative of the whole cohort.

Birth to Twenty study: 1990 (Richter, Norris, & De Wet, 2004). The transition from apartheid to democracy provided the initial context for this study from South Africa of 3,275 infants from pregnancy to adulthood. A broad range of topics were addressed including child and adolescent health and development, socio-economic factors and nutrition. While retention was reasonable the initial sample failed to recruit mother-child dyads from private delivery units. Other problems included high rural-urban migration. A range of demographic, biological, psychosocial and behavioural information was collected on the parents antenatally, with routine birth data recorded. The post-natal environment was assessed retrospectively at 6 months. Behaviour, language, mother-infant relationship and neurodevelopment were all assessed through fourteen data collection phases from birth until 16 years of age, including face-to-face developmental assessments at 6 months and 5 years. There was no assessment of child psychopathology during this period.

Copenhagen Perinatal Birth Cohort: 1959-1961 (Ventegodt, Flensborg-Madsen, Anderson, & Merrick, 2005). The sample consisted of 8,820 infants born in the city University College hospital of Copenhagen, Denmark (Raine, Breannan, & Mednick, 1994). A range of demographic, biological, psychosocial and behavioural information was collected on parents antenatally, and routine birth data recorded by physicians. The postnatal environment was assessed retrospectively at one year. Data collection continued until 33 years, but there was

no data collection between 6 years and 18 years, or between 18 years and 33 years. Full physical examinations were conducted at 1, 3, and 6 years, with neurodevelopment (neurological maturity, neuro-motor development, psycho-motor development) assessed at one year. Intelligence scores were measured at 18 years using the Børge Priens Prøve (BPP) test (Rasch, 1980), but only in 3773 male cohort members. There was no measurement of behaviour, language or psychiatric symptoms in the early years, making it difficult to answer questions on early onset mental health and neurodevelopmental disorders.

Danish National Birth Cohort: 1997 onwards (Olsen et al., 2001c). This study combines a birth cohort design with information from national health registers to examine outcomes that include behavioural disorders, and determinants such as social environment, genes, diet and infection (Olsen et al., 2001a). 100,000 pregnant women and their offspring constitute the sample. Despite this being a very large sample it only constitutes 30% of pregnant women in Denmark during the period of recruitment. A range of information on the prenatal environment was collected at three points during pregnancy, and birth data were obtained from records. Genetic analysis was conducted from maternal blood samples and umbilical cord blood. There is no detailed assessment of behaviour, language, social functioning, mental health or autism. A specialised autism health register could however be linked with the study data.

Generation R: 2002-2006 (Hofman et al., 2004). This current study of 9,778 infants from the Netherlands focuses on behavioural, cognitive and physical development and their determinants in a multi-ethnic population (Hofman et al., 2004; Jaddoe et al., 2006). Data are being collected in 17 phases through pregnancy and the first four years of life, and at the age of 5 years all children will be invited to visit the Generation R research centre for detailed assessments (Generation R study website, 2008). Enrolment, based on partial data, is 61% of those eligible (Jaddoe et al., 2006). A sub-sample of children of Dutch origin will undergo

more detailed assessment. A range of demographic, biological, psychosocial and behavioural information was collected antenatally, with physical examination of the baby at birth (full cohort) and at one month. Neurodevelopment was also assessed in the Dutch origin subsample at one month. Measures administered periodically to the whole cohort include the Child Behavior Checklist (Achenbach & Edelbrock, 1983) and the Infant Behaviour Questionnaire (Rothbart, 1981; Gartstein & Rothbart, 2003). While parent psychopathology is assessed there is no psychiatric assessment of the children and no measure of language or social functioning.

INMA (Infancia y Medio Ambiente): 2004-2005, (http://inma.imim.es/). This current Spanish multi-site study aims to examine the role of environmental pollutants on child development. A sample of approximately 3,300 pregnant women was recruited from various Spanish regions. Whilst each regional sample has been recruited from a population base, the focus varies between regions and some samples are selected (e.g., only mothers giving birth to boys were recruited in Granada). Outcomes under study include neurodevelopment, milestones, asthma and allergies while determinants include prenatal environmental factors (ultrasound and maternal urine). While there is data collection throughout pregnancy there is none between 12 months and 4 years of age. Neurodevelopment and social competence are measured. There is no measurement of mother-child relationship or psychopathology.

Mater-University of Queensland Study of Pregnancy: 1981-1983 (Najman et al., 2005). The original obstetric focus of the study gave way to issues of child psychiatry and mental health (Najman et al., 2005). While the sample of 7,223 infants was broadly representative of public patients, no private patients were recruited leaving 42% of hospital births not enrolled. Since private insurance to cover health care is widespread in Australia, public hospitals cater to a greater number of less well-off families with an over–representation of other health and social risk factors. Disproportionate attrition from lower socio-economic groups has further

reduced the representativeness of the sample. Psychosocial data were obtained from mothers during pregnancy, and birth data obtained from medical notes. Although data were collected 3-5 days after birth, the focus was on the mother's health until the next phase at 6 months. Following up to 14 years, child problem behaviour, language and cognitive development were measured by standardised instruments, including a face-to-face assessment of the child at 5 and 14 years, but there was no categorical psychiatric assessment. Lack of data collection between 6 months and 5 years means there are important gaps in developmental information crucial to the understanding of disorders of behaviour and social communication.

Northern Finland 1: 1966, (http://kelo.oulu.fi/NFBC). This birth cohort of 12,068 infants, from Oulu and Lapland in Finland, constitutes a representative sample. Demographic, psychosocial and behavioural data were collected antenatally, and routine birth data were recorded. No further data collection occurred until 1 year when a face-to-face 'developmental milestones' assessment (Isohanni et al., 2001) examined a range of features including neurodevelopment. Cognitive development and the presence of any major neurological deficits were recorded at 14 years. While the contribution of the study to the understanding of adult psychopathology has been significant there exist few relevant measures during infancy and no measures at all between the ages of 1 and 14 years, meaning the study is unable to address key questions about neurobehavioural development and associated disorders.

Northern Finland 2: 1985-1986 (Yliherva, Olsen, & Jarvelin, 2001). In a similarly designed study to its predecessor this cohort consisted of 9,479 infants at birth. Whilst some data (behaviour and cognitive development) were collected during school years (age 7 and 8), these data are not sufficient to answer key questions about neurodevelopment. Some nested case-control studies have revealed noteworthy findings on neurodevelopment and low birth

weight (Yliherva et al., 2001) and family interaction and behavioural problems (Taanila, Laitinen, Moilanen, & Jarvelin, 2002).

Norwegian Mother and Child Cohort (MoBa)/ Autism Birth Cohort (ABC) (Norwegian Institute of Public Health, 2005): Combining a prospective birth cohort and national registers this study focuses on development, birth defects, infections, neurodevelopment and asthma in a sample of 100,000 mother-child dyads (88,027 recruited to the end of 2007 (Norway Autism Birth Cohort (ABC) Study, 2008)). While this is a very large sample, and most pregnant women in Norway were invited to participate, enrolment was between 40% and 50% of pregnancies invited to participate in any one year, and so has to be regarded as a self-selected sample. Demographic, psychosocial, behavioural and biological measures are obtained antenatally and at birth (cord blood sample). Perinatal factors are assessed when the baby is 6 months old. A sub-study conducted from 36 months managed by Columbia University (Autism Birth Cohort (ABC)) focuses on autism. Antenatal measures largely concern physical and diet/feeding aspects and no in-depth psychosocial or mental health issues are addressed until age 3.5 years when clinical autism diagnostics are administered to potential cases and randomly selected controls. Parental mental health is not addressed in depth.

Port Pirie Study, Australia: 1979 (Baghurst et al., 1992). The main aim of this study was to provide evidence on the link between lead exposure in children born near a lead smelter and detrimental effects on cognitive, intellectual and behavioural development (Baghurst et al., 1992). Around 90% of pregnancies were enrolled in the study resulting in a sample of 723 infants. Blood samples were taken in pregnancy and at birth, with the perinatal environment assessed retrospectively at 6 months. While intellectual functioning, behaviour and development were measured, including face-to-face developmental assessments at 2, 4 and 7 years, the size of the sample is too low to study disorders of behaviour and communication.

Furthermore there was no psychiatric or mental health assessment. Infants at high risk of lead exposure cannot be said to be representative of the general population.

Cohorts recruited at birth

British Cohort Study 1970

(http://www.cls.ioe.ac.uk/studies.asp?section=0001000200020010). In order to make comparisons with the 1958 National Child Development Study cohort (see above), 17,198 children were enrolled at birth from across the UK and are still being followed-up (they are now 38 years old). The initial focus was on social and biological characteristics of mothers in relation to neonatal morbidity, with later data collection taking in broader social, physical and educational development. The enrolment rate was good (at 96% of all births), and efforts were made to include all types of hospital (i.e., private, NHS, military, prison) and home births, but only 65% of the sample was retained to 16 years (the last childhood data collection). The pre-/peri-natal environment (demographic, behavioural, medical) was assessed at birth, with no further data collection on the whole sample until 5 years (and again at 10 and 16 years). Data collected from subsamples at 22 months and 42 months included a face-to-face 'developmental screening questionnaire' which included some assessment of the child's motor and cognitive development. Behaviour problems, language, cognitive, and neurological development were assessed in the whole cohort using standardised instruments. There was no assessment of psychiatric symptoms and the lack of data collection within the first 5 years of life making it difficult to answer questions on early onset mental health and neurodevelopmental disorders.

Children's Health and Environment in the Faroes (CHEF) – Cohort 1: 1986-1987 (Weihe et al., 1994). A birth cohort of 1023 children born between March 1986 and December 1987 was established was followed up at age 7 and age 14 years. The focus was on intrauterine

methylmercury exposure, as measured by concentration in mothers' hair and cord blood at birth, and its relation to later development. Ninety percent of the original cohort was retained at age 7, but only 67% had full exposure data (Grandjean, White, Weihe, & Jorgensen, 2003). Eighty five percent of the survivors of the original cohort were retained at age 14 (Murata, Weihe, Budtz-Jorgensen, Jorgensen, & Grandjean, 2004). Studies showed an association between poorer neurological functioning and methylmercury exposure, but there were no measures of child psychopathology.

Christchurch Health and Development Study: 1977 (Fergusson & Horwood, 2001). This is the only study in this review in which overall child and adolescent mental health represented a key focus from the stage of the original design. The study is of 1,265 infants from Christchurch, New Zealand, followed from birth (Fergusson et al., 2001). Initial enrolment rates were good while attrition was disproportionately from lower and middle socio-economic groups. Annual data collection took place until the cohort members reached 21 years of age, at which point 80% (n=1011) of the original cohort was retained. A range of demographic, biological, psychosocial and behavioural information (including birth data) was collected from parents at birth, with the post-natal environment assessed retrospectively at 4 months. There were no standardised measures of behaviour, neurodevelopment, psychopathology and language in the pre-school years. Behaviour and language development were assessed through the school years, with parent-child relationship assessed at age 15-16 years. The Child Psychiatric Self-Rating Scale (Beitchman, Raman, Carlson, Clegg, & Kruidenier, 1985) was administered at age 9-10 years, and at age 18, participants were asked about psychiatric problems since the age of 16 using a questionnaire based on the Composite International Diagnostic Interview (CIDI) (World Health Organisation, 1993). There were no face-to-face clinical assessments of the participants' mental health. The relatively modest sample means that lower prevalence disorders such as autism were not studied.

Copenhagen County Child Cohort: 2000 (Skovgaard et al., 2005b). One of only two studies in this review with a focus on infant psychopathology and a detailed clinical assessment at 18 months, this study involved public health nurses and health registers following 6,090 infants from Copenhagen, Denmark, from birth. Within 2 weeks of birth, demographic, psychosocial and birth data were collected from mothers, and the child's health (including mental health domains) assessed. Through parent report, direct observation and standardized physical and developmental assessments, information was collected at three further points in the first 10 months on the general development of the child, the relationship between mother and child, and family relations (Skovgaard et al., 2005b). Specific developmental milestones (psychomotor development, language / communication appropriate for age, social and emotional state) were assessed at each of these early data collection points, and the mental health of the infant was assessed comprehensively, including domains of psychomotor regulation, eating, sleeping, language development, social interaction, emotional state and mother-infant relation (Skovgaard et al., 2005b). At 18 months 200 cases (identified through the public health nurse screening) and 200 randomly selected controls were subjected to detailed psychiatric and psychological assessment, including measures of autistic traits (Skovgaard, Houmann, & Christiansen, 2005a). This study offers rich information on the first year of life, with key papers on the reliability of diagnostic tools (Skovgaard et al., 2005a) and the prevalence of psychopathology (Skovgaard et al., 2007) in early childhood. Nevertheless, the lack of assessment between 18 months and the next phase at 5 years does not allow a full assessment of early risk and protective factors for childhood mental health problems.

National Child Development Study, 1958

(http://www.cls.ioe.ac.uk/studies.asp?section=0001000211130012). Originally conceived as the Perinatal Mortality Survey, this ongoing study recruited 98% of all births (17,414

children) in England, Scotland and Wales for one week in March 1958. Eighty percent of the sample was retained to 16 years and follow up continues. Midwives provided information on mothers' antenatal care, demographics, and birth data. The postnatal environment was not assessed as no further data were collected until the child reached 7 years. Parent interviews included questions on behaviour, family relationships and the child's health (including mental health), but only the child's physical health was assessed directly. Language and cognitive development was assessed and teachers completed standardised social adjustment and behaviour measures. There were no measures of child psychopathology.

National Institute of Child Health & Human Development (NICHD) Study of Early Child Care (SECC): 1991: (http://secc.rti.org/summary.cfm). 1364 babies born at 10 sites across the USA in 1991 were recruited to this study at birth. Unfortunately no data were collected (apart from recruitment information) until the end of the perinatal period. 1364 mothers were enrolled from 8986 giving birth in the sampling period. As well as conventional exclusion criteria (e.g., medical problems), children of mothers under the age of 18, mothers who were not fluent in English, and mothers living in neighbourhoods deemed unsafe for research assistants to visit were excluded from the study. At the first data collection (one month) infant temperament, maternal depression, parental stress, parental locus of control, parental relationship quality (as perceived by mother) and maternal separation anxiety were assessed, along with broader social and economic factors. Subsequently this cohort has been regularly followed up with a wide range of measures. In the early years these included the MacArthur Communicative Development Inventories, the Reynell Developmental Language Scales, the Strange Situation Technique, the Bayley Scales of Infant Development in the early years, as well as regular periods of observation of behaviour and environment. Later childhood data collection focused on children's lived experience, including friendships and school attainment, as well as direct measurement and observation of development progress and

behaviour. Psychiatric symptoms were regularly monitored using Achenbach's Child Behaviour Checklist, including at the most recent follow-up at age 15 years (2006).

Pacific Islands Families Study: 2000 (Paterson et al., 2002). Physical, neurological and behavioural development were studied from birth in a cohort of 1,398 infants born to at least one parent of Pacific Island ethnicity resident in Auckland, New Zealand (Paterson et al., 2002). Enrolment was approximately 80%. No antenatal data were collected. Child behaviour, language and neurodevelopment measures were completed in six data collection phases from 6 weeks to 6 years in addition to a number of other parental psychosocial measures. Children were assessed directly using the Bayley Infant Neurodevelopmental Screen at 12 months and during home visits at 2, 4 and 6 years. Further data collection is planned for when the children reach 9 and 11 years of age. The relatively small sample, and a lack of categorical psychiatric assessment would prevent questions about prevalence of psychiatric diagnoses and comorbidity being answered.

Pelotas Birth Cohort Study: 1993 (Victoria et al., 2006). Longitudinal epidemiological research is rare in developing countries and the focus of this Brazilian study was necessarily broad. Strong recruitment resulted in a representative sample of 5,249 infants, but only a sub-sample of between 13-20% was followed up and there was no data collection between 12 months and 4 years. Full follow-up has since re-commenced with data collection at age 11 and 15 years. No data were collected antenatally, although mother's behaviour during pregnancy (smoking, etc) was assessed at birth. While neurodevelopment was assessed there was no measurement of behaviour, language, social functioning, mother-infant relationship or psychiatric symptoms in the early years.

Key excluded studies

There were five studies which, although not fitting the inclusion criteria, are significant to the field and worthy of note here.

Dunedin Multidisciplinary Health and Development Study: 1972-1973. This was excluded from our analysis as the cohort was retrospectively identified (when the children were three years old), with the eligible population being those born within the defined dates and still resident within Dunedin. This ongoing study has gone to great lengths to retain its participants and at the 26 year phase collected data from 980 participants (96% of the living cohort) (Poulton et al., 2006). It has made an invaluable contribution to our understanding of gene-environment interaction in child psychopathology: Caspi et al (2002) showed that the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) appears to moderate the effects of maltreatment, in that high MAOA activity may be a protective factor in relation to abusive parenting. Further, Caspi et al. (2003) demonstrated a moderation of the association between childhood maltreatment and adult depression by the 5-HTT (serotonin transporter) genotype. The design, however, precludes answering questions about the associations between early neurodevelopment and later psychopathology.

Millennium Cohort Study: 2001 onwards: Focused on understanding the social circumstances surrounding birth and early childhood, this sample of 18,818 children drawn from all live births across the UK over 12 months was excluded from this review as the cohort was identified retrospectively from child benefit records at eight months. Nevertheless, a broad range of important data has been collected, including parental background, birth data, pre- and peri-natal environment, parents' mental health, maternal attachment, baby's temperament and behaviour. Children's cognitive development and emotional and behavioural problems and parenting were assessed at 3 and 5 years, and there are plans to continue to measure these in future sweeps. There are no plans to include a psychiatric assessment or any focus on rare

conditions such as autism. At the most recent sweep (5 years) 79.2% of the cohort were retained.

NBR & NIR Sweden study: 1973-1977: Information on 507,516 children born in Sweden between 1973 and 1977 was accessed through the National Birth Register and linked to corresponding records on the National Inpatient Register systems between 1987 and 1995. There were 238 cases of schizophrenia diagnosed within the cohort, with pre-eclampsia presenting an increased risk for such a diagnosis (Dalman, Allebeck, Cullberg, Grunewald, & Koster, 1999). However, as the schizophrenia diagnosis was made any time between the ages of 14 and 23 years of age, the extent to which this represents association with a *childhood* mental health problem is not clear from the published work.

Newcastle Thousand Families Study: 1947: All 1142 babies born in Newcastle upon Tyne in May and June 1947 were recruited in a study originally designed to focus on infant mortality and morbidity. A broad range of data was collected, and the study expanded, with children being followed up regularly (at least annually) until the age of 15 (at which point data were gathered on 67% of the original cohort; 28% had left Newcastle and were not followed-up until age 50) (Lamont et al., 1998). This study was excluded as no measures of childhood psychopathology, behaviour, parent-child interaction, language development or neurodevelopment were taken. IQ was measured at age 11 (the 'eleven plus' exam), however, and analyses conducted relating this to physical growth (Pearce, Deary, Young, & Parker, 2005).

Swiss Etiological Study of Adjustment and Mental Health (SESAM): (2007) onwards: This antenatally-recruited cohort study began in October 2007, but as yet there are no published papers. The study website (www.sesamswiss.ch, accessed 19th March 2009) indicates that recruitment rates were low and that work on the cohort is being discontinued.

Discussion

Our review shows that while there are a number of cohort studies examining child and adolescent mental health outcomes, there are relatively few that have recruited from birth or antenatally within a population base. Whilst the extant literature from these studies has taught us a great deal about child and adolescent mental health, they are limited in what they can tell us from this basis. Without recruitment prior to babies being born, there is no way of assessing the environment (including the parents' mental health and the home environment) as a true baseline, i.e., independently of the new baby. Without recruitment from a population base there is no way to answer questions about the dimensionality of putative risk factors for mental health problems. Where studies have met these inclusion criteria, there are often time gaps in data collection (see Fig. 1) that make it difficult to gain a full understanding of complex neurodevelopmental trajectories. Some studies have intensively gathered data in the first year or two of life, but then failed to follow children up until much later (e.g., Copenhagen County; Danish National Birth Cohort). On the whole, with the exception of five studies (ALSPAC, Birth to Twenty, Christchurch, Generation R and Port Pirie), there is little data collection between the ages of 1 and 3 years. Similarly, apart from three studies (ALSPAC, Birth to Twenty and Christchurch), later childhood is also somewhat overlooked. Annual data collection beyond the age of 5 is rare. In many studies, however, the time period assessing children in late childhood has not yet been reached.

Figure 1 about here

Further, it is relatively rare for studies to collect data on psychopathology in childhood. There are broader measures of mental health and wellbeing, such as parent self-report of perceived problems and more formal screening measures such as the Strengths and Difficulties Questionnaire (Goodman, 2001; Goodman, Ford, Simmons, Gatward, & Meltzer, 2003); but the direct clinical assessment of psychiatric symptoms is fairly rare. Some studies

only begin to ask questions about psychopathology when participants reach their teenage years, where self-report measures and routine data sources can be more easily employed.

It would seem then that there is a trade-off between regularity of data collection and focus of study. ALSPAC and Birth to Twenty have collected data on an annual basis on children who are now young adults, but these studies have had a broad focus. They tell us much about children's lives but in doing so cannot focus on every aspect of development. Sub-studies such as the ALSPAC Children in Focus cohort and nested sub-studies on high scoring cases such as that within the Copenhagen County study are a useful means to address this dilemma. Ideally, however, future research should aim to take in a large population with regular (at least annual) data collection and focus specifically on mental health outcomes. This is the best means by which we can expand our understanding of developmental trajectories of *all* children, thus enhancing our ability to help the most vulnerable.

Diagnostic categories, whilst an invaluable clinical tool, inevitably encourage a hypothetico-deductive form of reasoning. They are also useful tools in research, but as Pickles and Angold (2003) state, researchers need work on developing a more 'fluid set of tools' to allow us to better analyse and communicate issues of psychopathology. Clinical researchers working with prospective study designs have a responsibility to not be constrained by current thinking. The reality remains that we know relatively little about rarer disorders such as autism and reactive attachment disorder, and the clear presence of overlap between conditions means we are unlikely to be able to develop something approaching a 'clear picture' without taking a more open and inductive approach to formulating research questions.

Birth cohorts are used for a variety of purposes and this review highlights differences between cohort designs which may affect how their findings can be interpreted. This area of research often needs large sample sizes and the ideal design for a cohort investigating the full

breadth of childhood psychopathology would involve the entire population of an area born in a given time period. Studies such as the British Cohort Study very clearly achieved this, recruiting 96% of all births in England, Wales, Scotland and Northern Ireland within a single week. This study was however conducted in 1970, and it is unlikely that in the current climate such good coverage would be achieved. Other studies have taken longer to obtain very large cohorts. The Danish National Birth Cohort and the Norwegian Mother and Baby study have recruited very large samples from a population base. These large numbers were recruited by sampling a small percentage of births in any one time frame over a number of years. This means that they are ultimately only representative of a small proportion of all pregnancies within the target population over that time period. Only with very good routine data on the whole population, which both Norway and Denmark have, is it possible to say how representative these participants are of the general population. The Spanish INMA study has a widely dispersed sample that has been partially selectively recruited from target populations. Whilst there is no doubt that a wealth of important data can be obtained from this large multi-centre study, it may be difficult to make generalisations from the findings of this study to the broader population.

There are also many similarities in methodology between the cohort studies reviewed here, and it is possible that these can be utilised to generate larger datasets and possibly meta-analyses, especially in the case of regions where good routinely collected data are available. But as demonstrated in Tables 5 to 12, it is rare that similar measures have been used across cohorts. Any new cohort should be designed in the context of what data is already available and in consideration of methodology already being applied.

Swanson and Wadhwa (Swanson & Wadhwa, 2008) address critical issues which should be taken into account in birth cohort studies of developmental psychopathology. These include: the simultaneous assessment of putative risk factors in the same cohort; the longitudinal

assessment of environmental factors from before conception through pregnancy; foetal life, birth, and infancy; and finally the investigation of the interplay between gene and environment by the epigenetic modification of nuclear DNA and chromatin structure during critical periods in early development and over time and under various environmental conditions. These issues must all be considered in birth cohort studies if crucial details about child neurodevelopmental disorders are to be understood. Such studies however, are likely to be expensive. We have begun to make inroads into our understanding of gene-environment interactions. The Dunedin cohort in particular has made an invaluable contribution to our understanding of gene-environment interaction in the development of psychopathology, in particular interactions between MAOA polymorphisms and maltreatment in the development of conduct disorder (Caspi et al., 2002); between 5-HTT polymorphisms and adverse life events in the development of depression (Caspi et al., 2003); and between catechol-O-methyltransferase polymorphisms and cannabis use in the development of psychosis (Caspi et al., 2005) Ideally, future birth cohort studies will be structured so as to include all known potential risk/protective factors and confounders, begin in the antenatal period, continue with frequent measures throughout childhood of all the relevant variables and include regular in depth assessments of mental health outcomes in a population powered to examine both common and rare disorders. Clearly in any study, these considerations need to be balanced against cost. The use of excellent routine datasets, such as are available in Scandinavia and in some parts of the UK, can be a useful way of maintaining regular data gathering in large representative populations when regular face-to-face data gathering is unfeasible. Researchers nevertheless need to be aware of the dangers of very large studies yielding false positive findings, or findings which are statistically significant but of limited public health importance.

To date there is no single cohort that can tell us all we need to know about the full range of very early processes which may contribute to the development of problems with social relationships. For example, neurodevelopmental problems are more common in children living in situations of low environmental stimulation such as institutions (Rutter, O'Connor, & The English and Romanian Adoptees (ERA) Study Team, 2004). We do not yet know to what extent this observation is explained by genetics, the environment or their interaction. There is a lack of basic observation of children in the very early years in the existing studies and innovative methods for capturing early social interactions among large numbers of families need to be developed to tackle this issue.

Despite the issues raised in this paper regarding previous birth cohort research, it is clear that this is a methodology that continues to develop and thus enhance the knowledge base on child and adolescent mental health outcomes. This review demonstrates what birth cohort studies can add to cross sectional data. They allow for the investigation into factors that are not possible to examine in cross sectional studies, for example, risk factors, onset and early symptoms of neurodevelopmental disorders. Examining the methodology of previous studies allows this progress to continue and helps build the path for the development of an optimal birth cohort design and method in the future. In addition it leads to further questions regarding birth cohort studies, most notably the potential for a further systematic review examining the results of the studies reviewed in this paper.

Limitations

This review has set out to offer a comprehensive account of birth cohort studies derived from a population base that can answer questions on the precursors of child and adolescent mental health problems. We have however relied on the search term ‘birth cohort’ to identify what is a large and diverse body of work. Whilst this has been supplemented by secondary referencing and consultation with colleagues, the fact that some studies only came to light as

a result of this supplementary research means that the possibility always remains that further studies exist but have not been documented here. Furthermore, whilst every attempt has been made to identify all data collected within each study, including contacting study staff directly, there remains the possibility that important measures that would have informed this review have been inadvertently omitted. Similarly, although we applied a broad definition of 'child and adolescent mental health' (see Tables 5-12, online) this may not include all measures that may be of interest to all readers. The measures have been listed according to broad category, but we acknowledge there may be differences in opinion about the categorisation of some measures (e.g., whether to label as temperament or behaviour).

This review has focused on the measures used in birth cohort studies in relation to child and adolescent mental health outcomes, but has not explored the findings of these studies. To do so would have made this paper too lengthy, and so exploration could present an opportunity for future reviewers. This work could also be extended to a more critical review of the relationship between the asked questions, the methodology used and the obtained answers in birth cohort studies.

Conclusion

This review demonstrates that whilst there are a number of population-based birth cohort studies that measure mental health outcomes in childhood, no study gives a broad view of the development of child and adolescent psychopathology or of the spectrum of healthy and pathological social relationships.

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Table 1. ***Basic details of birth cohort studies***

Study Name	Pop. Location	Year of Cohort	Sample Size	point of enrolment	Focus of study	Key Reference
Amsterdam Born Children and their Development (ABCD)	Amsterdam, Netherlands	2003-2005	7,051	Antenatal	- ethnic differences in pregnancy outcome - nutrition and immunological status, psychosocial health and substance use - physical activity, work and workload	(van der Wal et al., 2006; van Eijsden, van der Wal, & Bonsel, 2006; Benhadi et al., 2007)
Avon Longitudinal Study of Pregnancy and Childhood	Bristol & Avon, UK	1990-1992	14,062	Antenatal	- biological, environmental, social, psychological and psychosocial factors - various health and development outcomes	(Golding et al., 2001)
Birth to twenty	Soweto & Johannesburg, South Africa	1990	3,275	Antenatal	- child and adolescent health and development - socio-economic, political, demographic and nutritional transition underway in South Africa	(Richter et al., 2004)

Study Name	Pop. Location	Year of Cohort	Sample Size	point of enrolment	Focus of study	Key Reference
British Cohort Study: 1970	UK	1970	17,198	Birth	- social and biological characteristics of the mother in relation to neonatal morbidity - to compare the results with those of the 1958 National Child Development Study - physical and educational development at age 5, physical, educational and social development at ages 10 and 16	(Maughan, Taylor, Taylor, Butler, & Bynner, 2001)
Children's Health and Environment in the Faroes (CHEF) – Cohort 1	Faroe Islands	1986-87	1023	Birth	- hazardous exposures to marine toxicants in the pre- and peri-natal period & possible early adverse effects on growth and development	(Grandjean et al., 1992)
Christchurch Health and Development Study (CHDS)	Christchurch, New Zealand	1977	1,265	Birth	- child and adolescent mental health - emotional and behavioural difficulties in middle childhood	(Fergusson et al., 2001)

Study Name	Pop. Location	Year of Cohort	Sample Size	point of enrolment	Focus of study	Key Reference
Copenhagen Perinatal Birth Cohort	Copenhagen, Denmark	1959-1961	8,820	Antenatal	- pre- and peri-natal conditions and their influence on children's development - various demographic, social and medical factors, including neurological and psychological development	(Raine et al., 1994)
Copenhagen County Child Cohort	Copenhagen, Denmark	2000 onwards	6,090	Birth	- mental health problems in infants and children	(Skovgaard et al., 2005b)
Danish National Birth Cohort (DNBC)	Denmark	1996-2003	100,000	Antenatal	- exposures include: social environment, genes, diet and infection - outcomes include: behavioural disorders, congenital malformations, cancer, asthma	(Olsen et al., 2001b)
Generation R	Netherlands	2002-2006	9,778	Antenatal	- physical, behavioural and cognitive development and their determinants - diseases in childhood	(Jaddoe et al., 2006)
INMA (Infancia y Medio Ambiente)	Spain	2004-2005	2,600 - 3,500	Antenatal	- prenatal environmental pollutants - neurodevelopment, milestones, asthma/allergies	URL: http://inma.imim.es

Study Name	Pop. Location	Year of Cohort	Sample Size	point of enrolment	Focus of study	Key Reference
Mater-University of Queensland Study of Pregnancy (MUSP)	Brisbane, Australia	1981	7,223	Antenatal	- medical and social factors associated with adverse pregnancy outcomes - health, development, learning and behaviour	(Najman et al., 2005)
National Child Development Study: 1958	UK	1958	17,414	Birth	- to examine the social and obstetric factors associated with stillbirth and death in early infancy	(Power, 1992)
The NICHD Study of Early Child Care and Youth Development (NICHD SECC)	USA	1991	1364	Birth	- the relationship between child care experiences and characteristics and children's developmental outcomes	(Stright, Gallagher, & Kelley, 2008)
Northern Finland Birth Cohort 1	Northern Finland	1966	12,068	Antenatal	- various demographic, social and medical factors - mental health in adulthood	(Rantakallio, Koiranen, & Mottonen, 1992)
Northern Finland Birth Cohort 2	Northern Finland	1985-1986	9,432	Antenatal	- various demographic, social and medical factors - mental health in adulthood	(Koivu, Hartikainen, Sipila, & Rantakallio, 1988)

Study Name	Pop. Location	Year of Cohort	Sample Size	point of enrolment	Focus of study	Key Reference
Norwegian Mother and Child Cohort Study (MoBa) / ABC Columbia	Norway	1999-2007	88,027	Antenatal	- demographic, social, environmental, nutritional factors - development, birth defects, infections, growth/obesity, neurodevelopment, asthma allergies, autism	(Norwegian Institute of Public Health, 2005)
Pacific Islands Families Study	Auckland, New Zealand	2000	1,398	Birth	- physical, neurological and behavioural development - cultural, economic, environmental and psychosocial factors	(Paterson et al., 2002)
Pelotas Birth Cohort Study 2	Pelotas, Brazil	1993	5,249	Birth	- various demographic, social and medical factors in a developing country, including psychological development	(Victora et al., 2007)
Port Pirie Cohort Study	Port Pirie, Australia	1979	831	Antenatal	- impact of lead exposure on childhood physical and neurobehavioural development	(Wigg et al., 1988; Tong, Baghurst, Sawyer, Burns, & McMichael, 1998)

Figure 1. ***Timeline for each included study***