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INVITED REVIEW

Birth cohort studies in psychiatry: beginning at the beginning

IAN COLMAN AND PETER B. JONES*

Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

INTRODUCTION

Longitudinal formulations of psychiatric illness have long been familiar. In the 19th century, Thomas Clouston wrote about developmental insanity in young men, presaging modern views of schizophrenia as having some of its origins or first manifestations in early life (Clouston, 1891; O'Connell *et al.* 1997). At the same time, Sigmund Freud was creating his system of psychoanalysis to understand hysterical conversion and other aspects of adult psychology as sequelae of early psychological events. Now, within an epidemiological and neuroscientific framework, we are beginning to understand that a variety of psychiatric disorders, including those of later life, such as cognitive decline and dementia may be the final common pathway of a long chain of mutable events (Richards *et al.* 2004). Just as in clinical neurology, where one is taught to place the causal lesion as high as possible so, too, in psychiatry we should look for the seeds of causality earlier rather than later in life.

The epidemiology of chronic physical illness in adult life has taken longer to catch on to this idea that the child is the father of the man, but we now know that events during the first weeks and months of fetal life may have dramatic consequences for health and disease in the remote future (Barker, 1993, 1994). Psychiatric epidemiology and chronic physical disease epidemiology are now exploiting similar paradigms and learning from each other, both running under the banner of life-course epidemiology. Long-term longitudinal studies are the bedrock of the life-course approach; some began as cohort studies set up by far-sighted individuals, others rely on ingenious reconstruction from disparate data sources, often with serendipity playing a part in terms of the early information not having been thrown away.

Recent years have seen numerous reports on psychiatric illness from longitudinal studies in which individuals have been followed for a few to more than 50 years. A Medline search for appearances of the MeSH term 'longitudinal studies' in *Archives of General Psychiatry*, *British Journal of Psychiatry*, *American Journal of Psychiatry*, and *Psychological Medicine* found 589 such studies between 1974 and 1983, 1065 between 1984 and 1993, and 1548 between 1994 and 2003; a steady rise. Here, we review some of the most influential. Our bias is towards birth cohort studies and their contribution to psychiatric epidemiology.

A variety of studies can be seen within the hypothetical structure of a birth cohort; including case-control studies. Even elderly subjects can always be seen as surviving fragments of a disparate group of births, and viewing them as such can be a useful barometer regarding the quality of study design; what sort of hypothetical population do these people represent? What differentiates one study from the next is whether data are collected prospectively, and at what point the prospective collection of data begins. Much of the groundbreaking work summarized in D. J. P. Barker's *Fetal and Infant Origins of Adult Disease* (Barker, 1993), for example, describes cohorts of individuals born in Hertfordshire in the first half of 20th century. The investigators identified the cohort based on birth records that included the key exposure of birth weight, and 'followed' them by tracing

* Address for correspondence: Professor Peter B. Jones, Department of Psychiatry, University of Cambridge, Box 189 Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.
(Email: pbj21@cam.ac.uk)

them through administrative health records until their death. There are older examples in psychiatry, such as Robins' seminal study of the fates of boys referred to a child guidance clinic (Robins, 1966). These studies exploit the efficiency of the case-control design by using contemporaneously collected exposure data but a prospective, albeit historical follow-up component.

Classical cohort studies tend to identify their populations at risk according to a specific exposure at the inception point of the study; exposed and unexposed individuals may have been born over a wide time-frame and so subject to a variety of age, period and cohort effects in addition to the effect of interest. However, many large cohorts are age-sensitive, in that the exposures or mechanisms of interest occur only at specific times of life to begin following a cohort. For example, Goodyer and colleagues have followed cohorts of school-aged children in the study of adolescent psychopathology, providing a better understanding of the endocrine system in the pathogenesis of depression (Goodyer *et al.* 1998, 2000, 2001, 2003). In essence, these are birth cohorts, picked up by the researchers later on in life; those missed person-years remain obscure unless filled in by prospective data that happened to have been collected, such as prior school records, or by the introduction of a retrospective element.

In young adulthood, longitudinal studies of military conscripts in Sweden and Israel have yielded important findings regarding precursors of schizophrenia (Andréasson *et al.* 1987; Lewis *et al.* 1992, 2000; David *et al.* 1997; Malmberg *et al.* 1998) and affective disorders (Zammit *et al.* 2004). Starting with illness as the exposure, studies of military conscripts in Norway have illuminated the long-term outcomes of alcohol abuse (Rossow & Amundsen, 1995, 1997). At the other end of the age spectrum, longitudinal cohort studies of the elderly, notably the Medical Research Council Cognitive Function and Ageing Study (Neale *et al.* 2001) and the Canadian Study of Health and Aging (Rockwood *et al.* 2000; Lindsay *et al.* 2002; St John *et al.* 2002), have produced important results regarding the onset and progression of dementia. All these studies can be seen, conceptually, within the birth cohort paradigm with subjects being survivors, in terms of life and residence, of the original set of births.

The ideal point to begin following a cohort is at birth, rather than conscription; much happens before this in terms of the factors associated with survival and risk of disease. If individuals can be followed from before birth, so much the better; the justification for inclusion being merely that subjects existed and so were at risk of an outcome. A birth cohort that is sampled from the general population theoretically follows those with all likely exposure levels, with all likely risk factor combinations, for all likely outcomes throughout life. It is possible, if a birth cohort were completely comprehensive, to study all risk factors for all diseases, and all possible mechanisms by which disorder starts, progresses, remits, and relapses.

This review will focus on six cohorts of individuals followed from birth that have had a significant impact on psychiatry: British cohorts of people born in 1946 (the National Survey of Health and Development; Douglas, 1964, 1968; Wadsworth, 1991), 1958 (the National Child Development Study; Butler & Bonham, 1963; Ferri, 1993), and 1970 (the British Cohort Study; Chamberlain *et al.* 1975; Brewer *et al.* 1982); New Zealand cohorts of people born in Dunedin during 1972–1973 (Dunedin Multidisciplinary Health and Development Study; McGee & Silva, 1982; Silva & Stanton, 1996), and Christchurch in 1977 (Christchurch Health and Development Study; Fergusson *et al.* 1978; Fergusson & Horwood, 2001); and the Northern Finland cohort of people born in 1966 (Rantakallio, 1969, 1988). In addition, we will make mention of another birth cohort we expect to make significant contributions to psychiatry in the coming century: the Avon Longitudinal Study of Parents and Children, a cohort of people born during 1991–1992 (Golding, 1990). These are all studies of many aspects of the lives of individuals distinguished only by being members of the general population born at a particular time and place; all life is there. We take a page from schools of business management and concentrate on the strengths, weaknesses, opportunities and threats inherent in using these cohorts that all show these characteristics.

STRENGTHS OF BIRTH COHORT STUDIES

A simple, yet compelling strength of birth cohort studies is that the prospective collection of data covers all, or the majority of the period of risk during which causal processes may accumulate. Furthermore, the design minimizes bias associated with recall. Recall bias has had a significant effect on epidemiological studies in many research areas, and psychiatry is no exception. For example, recall bias may explain the apparent 'cohort effect' (Klerman & Weissman, 1989) involving enormous increases in the prevalence of depression in individuals born in each successive decade of the 20th century. Statistical models have shown that a relatively low rate of recall failure (i.e. individuals not recalling symptoms that would indicate a major depressive episode during their lifetime) could explain the observed cohort effect (Giuffra & Risch, 1994; Patten, 2003).

While it may seem unlikely that people could forget something as significant as a major depressive episode, there is evidence that this is a common occurrence. Newman & Bland, in a community study of the incidence and prevalence of major psychiatric disorders in Edmonton, reported that 9·5% of individuals who were diagnosed with a lifetime history of depression at one point were not diagnosed with a lifetime history of depression at a mean of 2·8 years of follow-up (Newman & Bland, 1998). Similarly, Simon *et al.* reported on prevalence of depression across age groups. Regardless of age, individuals were most likely to report the first onset of their depression in the previous 5 years, suggesting that either onset age is decreasing for younger generations, or, more likely, that older cohorts are not correctly recalling earlier episodes of depression (Simon *et al.* 1995).

This is a salutary lesson for truly prospective, rather than reconstructed cohorts in terms of filling in missing data with retrospective information. Sacker & Wiggins (2002) approached the problem with the preferable design using data from the Malaise Inventory in the 1958 and 1970 British birth cohorts. By using the same instrument at similar ages, in two cohorts born 12 years apart, the investigators were able to analyse the effects of cohort, age, and period of birth. They concluded that a cohort effect was present, with higher rates of psychological distress in the 1970 cohort, though the effect was not nearly as dramatic as had been reported in earlier studies of major depression.

Given that prospectively collected data is preferable to retrospective data, a problem arises when there is a long latent period (usually years) between initial exposure and subsequent outcome. Fortunately, since the middle of the last century the foresight of investigators has allowed for long-term associations to be identified using prospective data from birth cohorts. For example, more than 25 years after the collection of birth-weight data, investigators have been able to show that low-birth-weight individuals had a higher risk of developing schizophrenia in the 1946 British birth cohort (Jones *et al.* 1994) and the 1966 Northern Finland birth cohort (Jones *et al.* 1998), and a higher risk of developing depression in the 1970 British birth cohort (Gale & Martyn, 2004).

Another benefit of collecting data prospectively over a long period of time is that you can eliminate any non-systematic errors caused by people simply being unable to recall details that seemed trivial at the time. Few parents might remember if their 36-year-old daughters bit their nails at age 6 years, for example, because it may not have seemed important at the time. Data from the 1946 British birth cohort, however, showed that nail-biting in 6-year-old girls was predictive of adult psychiatric disorder 30 years later (Rodgers, 1990).

A key additional strength of prospective collection of data is that it can aid in the assessment of causality. That a cause must precede its effect is obvious, but in psychiatry outcomes often evolve over some time rather than being ictic events, so establishing time-course is difficult or impossible in cross-sectional or retrospective studies. The use of prospective data from birth cohorts can confirm the temporal sequence of events, and confirm whether this particular criterion for assessing causality has been met.

The association between cannabis and schizophrenia is a good example. Andréasson *et al.*, for example, reported a strong association between cannabis use and schizophrenia among Swedish conscripts (Andréasson *et al.* 1987), however it was unclear if the cannabis use preceded the development of symptoms of

schizophrenia; both occur in young people and either may lead to the other. Data from the Christchurch and Dunedin birth cohorts have shown that adolescent cannabis users free of psychotic symptoms were significantly more likely to show later symptoms of schizophrenia (Arseneault *et al*. 2002; Fergusson *et al*. 2003*b*), providing much stronger evidence for a possible causal role for cannabis use in the development of psychosis.

Similarly, numerous cross-sectional studies have reported an association between marital status and psychological health where cause and effect may operate in either direction. Hope *et al*. investigated this association using data from the 1958 British birth cohort, searching for a causal link that may show a protective effect of being married (Hope *et al*. 1999). They concluded however, that individuals in poor psychological health self-select themselves away from marriage, refuting theories of the protective effect of marriage and adding a level of detail that may have been missed in other designs. The links between cigarette smoking and depression have been shown to be similarly complex (Fergusson *et al*. 2003*a*).

Last, the cohort design means that many outcomes can be assessed. This is a double-edged sword for psychiatry. On the one hand, investigations of novel dimensional or categorical outcomes such as mental 'health' rather than illness can be explored (Huppert *et al*. in press). On the other hand, the information that happened to have been collected before anyone had that bright idea may simply be inadequate in content or psychometric domains to support such new approaches; for the most part, one has to rely on what has been collected. Furthermore, while many morbid conditions are common, others, such as schizophrenia, OCD or other syndromes, are rare. This strains statistical power in birth cohorts. This introduces other weaknesses of the paradigm.

WEAKNESSES OF BIRTH COHORT DESIGNS

The key weakness of cohort studies, as in any observational study, is that people are not randomly assigned to exposures; life is not like that. Consequently, observed associations may be confounded by an unmeasured factor that would better explain the finding; residual confounding is rife.

Random assignment would ensure that all unmeasured confounding factors were equally distributed between comparison groups. Consequently, it has been commonly suggested that randomized controlled trials present superior evidence to observational studies, and this has been supported by reviews showing increased treatment effects in non-randomized studies of clinical interventions (Sacks *et al*. 1982; Chalmers *et al*. 1983; Colditz *et al*. 1989; Miller *et al*. 1989). This underlines that care is needed in interpreting results where residual confounding may be playing a potent though undefined, or unimagined role.

A second weakness of birth cohorts is that while they do attempt to prospectively collect information on individuals throughout their lifetimes in order to create a picture of the life course, it is not feasible to do that comprehensively. Birth cohorts collect information at specified times throughout cohort members' lives, and use snapshots of these epochs to describe a lifetime. In addition, it is common to collect retrospective data about events that have happened in the intervening months or years since the previous collection time. For example, in assessing common mental disorder at age 43 years in the 1946 British birth cohort, a scale was used that asked about the presence of symptoms in the 12 months prior to the interview (Lindelow *et al*. 1997). The perfect study would monitor all individuals all the time. However, this is clearly unfeasible and undesirable, and would defeat the object of keeping the samples representative of the original cohorts (Wadsworth *et al*. 2003) – we would not expect people who do not mind being constantly monitored to be representative of most populations.

OPPORTUNITIES FOR BIRTH COHORT STUDIES

Opportunities abound for future research within longitudinal birth cohort studies. Notwithstanding the problems of cross-sectional assessment to infer to follow-up epochs, several studies now have multiple measures over long periods and so can begin to examine dynamic processes over time, rather than multiple associations between

two events regardless of how far apart those have been. We can now model the developmental pathways, themselves, that may lead to mental disorder, rather than cross-sectional evidence of their existence; it is like being able to thread pearls onto a string and study the whole necklace, not just the components.

The wealth of data investigating developmental pathways has focused on schizophrenia where there were specific hypotheses regarding early insults and psychosis in early adult life (Lewis & Murray, 1987; Weinberger, 1987) just as some of the major birth cohorts were in the period of risk for the disorder. This coincidence meant that information collected years before on early development could be used to test specific hypotheses in a taxing setting. The results supported a developmental view of schizophrenia (Done *et al*. 1994; Jones *et al*. 1994, 1998) and, because of the continuous data collected in the early years, indicated a widespread, though subtle effect, rather than a major developmental insult in a minority (Weinberger, 1995; Jones & Tarrant, 1999). This view has been replicated in the Dunedin (Cannon *et al*. 2002) and Northern Finland birth cohorts (Cannon *et al*. 1999; Isohanni *et al*. 2001), reconstructed birth cohorts (Cannon *et al*. 2003), and extended to embrace affective disorder and anxiety (van Os *et al*. 1997; Sigurdsson *et al*. 2002).

Collecting data on multiple factors that may contribute to disease causation allows researchers to integrate them into an overarching life-course model that can identify pathways from conception to adult disease, allowing associations between early-life risk factors and adult disease to be tested, while including possible confounding factors throughout the lifetime (Ben-Shlomo & Kuh, 2002). Isohanni *et al*. used results from the numerous studies of schizophrenia in the 1966 Northern Finland birth cohort to create a life-course model of schizophrenia (Isohanni *et al*. 2000), linking psychosocial and biological risk factors to deterioration of functionality in the prodromal period and progression of the disease. This creates the setting for more complex modelling using methods such as structural equation modelling and path analysis.

Fergusson *et al*. recommended this life-course approach to modelling and measuring the many factors that contribute to suicidal behaviour in adolescents and young adults (Fergusson *et al*. 2000). Using data from the Christchurch birth cohort, they were able to incorporate time-varying data on social background, parental and family factors, individuals' adjustment, personality, intelligence, mental health, and stressful life events, into a dynamic model that describes several pathways to suicidal behaviour. A similar approach has been taken to psychosomatic disorder in the 1946 British birth cohort (Neeleman *et al*. 2002).

Recently, data on genetic factors have been incorporated into pathway models of disease causation using birth cohort data. It has been well established, for example, that certain individuals become depressed after a stressful life event while others do not. Van Os & Jones, using data from the 1946 British birth cohort, showed that early-life risk factors may modify person–environment interactions prior to onset of affective disorder in adulthood, and suggested that there may be a hereditary aspect to sensitivity to stressful life events (van Os & Jones, 1999). Caspi *et al*. recently confirmed that such a link could be explained by a genetic difference, using data from the Dunedin birth cohort (Caspi *et al*. 2003). They identified a genetic difference with regards to serotonin transport between groups that became depressed after a stressful life event *versus* those who did not, suggesting an explanation as to why individuals respond differently in the face of life events that are, in general, far more common than their adverse sequelae.

A life-course modelling approach, with the ability to integrate various factors, ranging from genetic differences and developmental markers to social environment and stressful life events in adulthood, can only benefit our understanding of the complex pathways to mental illness. Longitudinal birth cohorts, with the diversity of information collected across the lifetime, provide the ideal opportunity to study such models.

Beyond the benefits of using birth cohort data to examine pathways to onset of mental disorder, birth cohorts also provide opportunities to create models of disorder progression and remission. Repeated measures of the same disorder or disease allow for modelling of chronicity over time, differing onset times, differing remission times, and other aspects associated with disease status over the lifetime. Jaffee *et al*.

investigated early-life risk factors for depression in the Dunedin birth cohort, comparing subjects with adolescent-onset depression *versus* adult-onset depression (Jaffee *et al*. 2002). Based on differing risk factors depending on onset time, the investigators concluded that juvenile onset depression may be a different disorder than adult onset depression. In a similar study, Paykel *et al*. studied early life risk factors for common mental disorder in the 1946 British birth cohort, comparing onset and remission of disorder from age 36 to age 43 years (Paykel *et al*. 2001). They were able to identify several factors that differentiated those with earlier onset *versus* later onset, and those whose disorder persisted at the later age *versus* those whose disorder was in remission.

Studies of onset and remission that point to heterogeneous disease courses over time within the same disorder support the concept of longitudinal phenotypes, rather than the cross-sectional classification of disorder; two time-points are all that is needed. Kim-Cohen *et al*. (2003) reported that 74% of adults with a psychiatric disorder at age 26 years in the Dunedin birth cohort had a diagnosed disorder by the age of 18 years, and 50% had a diagnosed disorder by age 15 years. Similarly, Poulton *et al*. (2000) reported that children in the Dunedin birth cohort who reported psychotic symptoms (delusional beliefs and hallucinations) at age 11 years were 16 times more likely to have symptoms associated with schizophreniform disorder at age 26 years. Among the 'cases' at age 26, 42% had reported a psychotic symptom at age 11 years.

Multiple measurements over time allow for even more complex longitudinal models. Croudace *et al*. used data from six time-points in the 1946 British birth cohort in a latent class analysis of childhood night-time bed wetting (Croudace *et al*. 2003). At six different ages up to the age of 15 years parents were asked whether the child had wet the bed in the previous month. Longitudinal latent class analysis and latent class growth analysis identified four distinct developmental trajectory classes: chronic bed wetting, delayed acquisition of bladder control, late onset of bed wetting after initial acquisition of bladder control, and normal development. Future studies can investigate associations between the various developmental classes and other aspects of mental health during this time, differences with regards to risk factors for the classes, and mental health outcomes associated with the different classes. Similar longitudinal phenotypes for anxiety and depression throughout pregnancy and the puerperium were recently suggested (Heron *et al*. 2004) using data from the Avon Longitudinal Study of Parents and Children. This is a new way to approach developmental, psychological and psychiatric phenotypes as characteristics that are seen only with the long-view, rather than as cross-sectional or permanent phenomena. It is another way to carve pathology at the joints and, being closer to reality, may lead to new insights to causation.

Data such as these suggest that the study of mental disorder over time is appropriate and necessary, despite a relative paucity of such research to date. Again, longitudinal birth cohorts, with repeated measurements of mental disorder across the lifetime provide excellent opportunities for such research.

THREATS TO BIRTH COHORT STUDIES

A key threat to much epidemiological research, particularly longitudinal studies and birth cohorts, is restriction on the use of such data due to concerns about confidentiality of the individuals being studied. Laws such as the UK Data Protection Act of 1998 and some European legislation create several barriers for researchers wishing to work with sensitive personal information. This is particularly problematical for those wishing to link administrative data from different sources, where legislation may prevent linkage of data that was collected for non-research purposes. From the cohort member's point of view, concerns about privacy are understandable; a lifetime's worth of personal detail is in the balance. The incorporation of genetic data is likely to increase the sensitivity. These concerns are consistently reviewed by research ethics committees. It is incumbent upon any research group administering longitudinal cohort work to promote the benefits of such research to the participating community, and to make every effort to ensure that data protection is maintained. New developments in information technology and biometric, including genetic measurement and routine health outcome data in the NHS could and should be a massive

opportunity, but we feel this current suspicious, litigious and short-sighted climate eclipses this.

Other threats include the vagaries of long-term funding for any research, let alone for studies that, by definition, may require consistent resources for decades, during which time they must pay attention to the competing demands of data collection, storage, management, and scientific enquiry that demands publication and impact. That very long timescale presents further difficulties; science evolves rapidly and may overtake the reasons for which information was collected. Despite this hostile context, the Millennium Birth Cohort of some 20 000 babies born in the UK during 2001 has begun charting many aspects of their lives over time (Smith & Joshi, 2002).

CONCLUSION

Along with other areas that have embraced a life-course view, the future contribution to psychiatry from general population cohorts followed from early life will grow. The confluence of cohorts that have lived through the period of risk for major psychiatric disorders including cognitive decline, the advent of new hypotheses, statistical models that capture change over time, opportunities for linkage to health outcome data and enhanced information technology, combined with relevant new information from genetics, make this an exciting time. Perhaps there will not be another period where this could occur in such an explosive manner, owing to the increasing constraints upon the developments of new cohorts. This puts the onus on current researchers to ensure that our hypotheses match the opportunities, and to influence a broader constituency to ensure that they can be tested.

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DECLARATION OF INTEREST

None.

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