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Invisible children: attempting to engage the most vulnerable families

Cullen *et al*[1] describe childhood antecedents of schizophrenia: such prospective studies are rare. Retrospective research suggests that as the number of adverse childhood experiences increases, so does the risk for health problems, including alcohol misuse, ischaemic heart disease, suicide attempts and externalising behaviours.[2,3] However, retrospective studies are prone to the biases associated with recalling early childhood. The best way to fully understand the mechanisms underpinning the relationship between adverse childhood experiences and later development is to follow children prospectively from early childhood.

We had a unique opportunity to achieve this in Glasgow because of the existence of the Women's Reproductive Health Service (WRHS), which provides antenatal care for some of the most vulnerable women in Glasgow: those affected by problem drug or alcohol use or significant mental health or personality problems. This cohort is well characterised in terms of family adversity.

We conducted a feasibility study to see whether it was possible to assess the mental health of the children of very vulnerable mothers. We selected a random sample of ten women who had received antenatal care from the WRHS 7 years earlier. Of the ten children targeted, one was deceased, two had been adopted and one was uncontactable because the mother was in a woman's refuge in a secret location. Of the remaining six, three opted out, one was uncontactable despite repeat attempts, and of the two whose mother provided consent, one then became uncontactable and the last opted out. Each woman received a minimum of ten phone calls and five attempted visits with a letter left each time (unless they had opted out in writing or by phone). Despite two members of staff working full time for 8 weeks, it was not possible to conduct any mental health assessments on these children of very vulnerable mothers. Our research team were able to meet with only two out of our target sample of ten women and did not succeed in assessing any of the children. In other words, despite persistent phone calls and home visits, eight of these vulnerable women and all of their children remain invisible.

The considerable resources available to our research team – including the potential to make multiple phone calls and visits – are not usually open to healthcare or social-care professionals. The question we then have to ask is, how do we reach these most vulnerable of families and safeguard the health of their children?

1 Cullen AE, Fisher HL, Roberts RE, Pariante CM, Laurens KR. Daily stressors and negative life events in children at elevated risk of developing schizophrenia. *Br J Psychiatry* 2014; **204**: 354–60.

2 Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. The relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) study. *Am J Prev Med* 1998; **14**: 245–58.

3 Hillis SD, Anda RF, Felitti VJ, Marchbanks PA. Adverse childhood experiences and sexual risk behaviours in women: a retrospective cohort study. *Fam Plann Perspect* 2001; **33**: 206–11.

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Authors' reply: Notwithstanding the logistical and ethical issues that make this sensitive research difficult to accomplish, we agree that prospective investigations of children followed from early childhood offer the best prospect for identifying mechanisms underpinning the relationship between childhood adversity and later outcomes such as mental health, social functioning, and educational/occupational attainment.

In response to the query regarding how this important research might be achieved given the challenges Sim *et al* identified, we suggest that longitudinal, population record-linkage studies offer excellent capacity to examine these relationships in an unbiased, inclusive, and ethical manner. One such investigation is the New South Wales Child Development Study (http://nsw-cds.com.au) based at the University of New South Wales. This is a longitudinal investigation following the development of a cohort of 87 026 children who entered full-time schooling in 2009 (representing 99.9% of the population). Via local record-linkage infrastructure provided by the Centre for Health and Record Linkage (http://www.cherel.org.au), and operated under strict privacy provisions, anonymised multi-agency records on the children (including health, education, welfare, birth, and developmental records) have been combined by researchers with records on their parents (including health and criminal records).

As part of this study, diverse measures of childhood adversity are available from population-based government child-protection files. Records were available for 3926 children (4.5%) in the cohort by the age of 5 years. These records, in combination with linked information on mental health and well-being outcomes in childhood (and, in due course, in adolescence and adulthood), offer an excellent opportunity to determine the childhood, adolescent, and adult sequelae of early exposure to adversity. Publications from the initial phase of the investigation (spanning birth to 5 years in the population cohort) are currently in preparation.

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The developmental trajectory of bipolar disorder

The article by Duffy *et al*[1] in the February issue tests evidence for a clinical staging model of bipolar disorder for the offspring of parents with lithium-responsive illness and the offspring of parents with lithium-non-responsive illness.

In their analyses, Duffy *et al* were unable to show a statistically significant difference for the risk of any psychiatric disorder between both subgroups of offspring. Yet they still conclude that the offspring of parents with lithium-non-responsive illness manifest neurodevelopmental disorders in childhood and psychotic disorders in young adulthood. A second problem is that the neurodevelopmental disorder category included cluster A

traits, which do not readily fit with the others (attention deficit hyperactivity disorder (ADHD) and learning disabilities). A third problem is that schizoaffective disorder was included among the bipolar spectrum disorders in the analyses, a decision that requires further justification.

A fourth problem is that, as described in a previous article,[2] a diagnosis of bipolar affective disorder not otherwise specified was given to participants who presented with manic symptoms meeting threshold DSM-IV diagnostic criteria but not minimal duration criteria. It is possible that this was the reason for a statistically significant difference in the cumulative incidence of bipolar spectrum disorders between the offspring of well parents and the offspring of parents with a bipolar disorder. Finally, 23% of participants in the group of offspring of a parent with bipolar disorder 1 were recruited within families, making it unclear how many participants had a parent who did not have the disorder.

1 Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. *Br J Psychiatry* 2014; **204**: 122–28.

2 Duffy A, Alda M, Crawford L, Milin R, Grof P. They early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disord* 2007; **9**: 828–38.

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Authors' reply: The clinical staging model proposed represents an aggregate view based on results from an ongoing, prospective study of a unique, high-risk cohort. In prior analyses, we found evidence that ADHD and other childhood neurodevelopmental presentations occurred at a higher unadjusted rate in the offspring of parents with lithium-non-responsive illness compared with the offspring of parents with lithium-responsive illness.[1,2] In this updated analysis, instead of unadjusted lifetime rates we used cumulative incidence, which takes into account censoring and variable age at last assessment and Cox proportional hazard models adjusted for sibling correlation, gender and socioeconomic status. With longer observation, the unadjusted rate of psychotic disorders is now significantly elevated in the offspring of parents with lithium-non-responsive illness compared with the offspring of parents with lithium-responsive illness.

Second, cluster A traits and cognitive deficits are known antecedents to psychotic disorders and therefore we argue that these do in fact 'fit' with ADHD and learning disabilities as early risk syndromes in this high-risk population.[3] Third, schizoaffective disorder was included as an end-stage illness in this analysis given the overlap between schizoaffective and psychotic bipolar disorders.[4] Fourth, all offspring (control and high-risk) were assessed in the same way and all assessments were reviewed masked to family affiliation and diagnoses made by consensus using the same criteria. Therefore, the difference in rates of bipolar disorder not otherwise specified or any other diagnosis cannot be explained by modified diagnostic criteria for high-risk offspring as speculated by Chenard-Poirier & Paris.

Finally, given the high heritability and estimated likelihood that recurrent major depression in these families reflects the bipolar diathesis,[5] we expanded recruitment to include the offspring of parents who were siblings of the original bipolar proband and who themselves met lifetime criteria for bipolar disorder or recurrent major depression ($n = 20$). Therefore, every high-risk offspring had one parent with a bipolar or bipolar-related recurrent major depressive disorder. We thank Chenard-Poirier & Paris for raising these points and the *Journal* for allowing us to provide this clarification.

1 Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. *J Affect Disord* 2010; **121**: 127–35.

2 Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disord* 2007; **9**: 828–38.

3 Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res* 2004; **71**: 405–16.

4 Pearlson GD, Ford JM. Distinguishing between schizophrenia and other psychotic disorders. *Schizophr Bull* 2014; **40**: 501–3.

5 Blacker D, Lavori PW, Faraone SV, Tsuang MT. Unipolar relatives in bipolar pedigrees: a search for indicators of underlying bipolarity. *Am J Med Genet* 1993; **48**: 192–9.

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An oversimplification of psychosis, its treatment, and its outcomes?

Jauhar *et al*'s meta-analysis[1] of randomised controlled trials in cognitive–behavioural therapy for psychosis (CBTp) is broadly consistent with previous results:[2] that is, there is an overall significant but modest impact on psychotic symptoms, with blinded studies showing lower effect sizes than those that are not blinded. However, there are a number of problems with this study and especially with its conclusions.

Jauhar *et al* conclude that they find the advocacy by government (including NICE) for CBTp 'puzzling', bearing in mind the low effect sizes found for psychotic symptoms. However, I find it puzzling that the authors comment on NICE recommendations, since a third of the studies included for their overall symptoms analysis (12/34) were not based on therapies recommended by NICE in the first place (based on what we know is effective from the literature so far): they were either group or brief CBT studies. Three further studies were in Chinese, so their relevance to NICE recommendations is hard to tell.

It is a testament to the far-reaching effects of CBTp that the analyses revealed any effects at all, since the authors looked at outcomes that were not always targeted by the therapy. For instance, only a few of the 34 studies included for negative symptoms actually targeted such symptoms specifically. Furthermore, severity of positive symptoms/hallucinations was used as the outcome for studies that did not hypothesise changes in psychotic symptoms since the target was on compliance with command hallucinations,[3] emotional dysfunction,[4] or social functioning.[5] By contrast, outcomes on depression, anxiety or distress as a result of psychotic symptoms, and trials targeting self-esteem, post-traumatic symptoms, suicidality, or substance misuse, which are all main and legitimate targets in CBTp, were excluded.

The criteria for studies to be included in the final analyses were idiosyncratic. Perhaps the most surprising was the decision to exclude studies that targeted hallucinations specifically from their positive symptoms analyses. A separate 'supplementary' meta-analysis was carried out for those studies, with an effect size of 0.34, which is not reported in the abstract (where only the – lower – 0.25 effect on positive symptoms is reported). Clinicians familiar with clinical presentations of patients with psychosis might be surprised at their rationale for excluding trials because patients had a dual diagnosis, or had medication-resistant psychotic symptoms but no further diagnosis specification. None of the follow-up data available was included, meaning that the