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# Pre-morbid fertility in psychosis: Findings from the AESOP first episode study ☆

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ABSTRACT

Individuals with psychotic illnesses are known to have a reduced fertility. It is unclear whether this is due to biological or social factors. Most fertility studies have been conducted in chronic schizophrenia, where confounders like medication and hospitalisation make this difficult to elicit. A less severe reduction of fertility has been observed in some ethnic minorities, but results are inconsistent.

We sought to investigate pre-morbid fertility in an ethnically diverse sample of individuals with first-onset psychosis. Data were derived from 515 people with a first psychotic episode (FEP) and 383 controls. We made case–control comparisons of differences in the proportion of those with children (fertility rates) and mean number of children (MNC). Analyses were then stratified by diagnosis, gender and ethnicity, and adjusted for potential confounders.

We found that FEP showed a reduced fertility rate (age-adjusted OR of having children 0.47 [95% CI = 0.39, 0.56]), irrespective of diagnosis, and there was little evidence of confounding by gender, ethnicity, religious background, education level, or history of past relationships (fully adjusted OR = 0.55, 95% CI = 0.37, 0.80). Women had a somewhat greater reduction in fertility rates than men (Men: age-adjusted OR 0.61 [95% CI 0.42, 0.89]; Women: age-adjusted OR 0.46 [95% CI 0.31, 0.69]) and we could not find any evidence of ethnic differences in the degree of fertility reduction. FEP who had previously experienced a stable relationship had an MNC that was comparable to that of the general population and had a later onset of illness.

This is the largest case–control study to date to investigate fertility in first-onset psychosis. Our data suggests that fertility is affected, even prior to the onset of a psychotic illness, and there are likely to be biological and environmental factors involved, but the former seem to have a stronger influence.



## 1. Introduction

Individuals suffering from non-affective psychosis, particularly schizophrenia, have long been reported to have reduced fertility (Bundy et al., 2011) and this is most marked in men (Vogel, 1979; Nanko and Moridaira, 1993; Nimgaonkar et al., 1997; McGrath et al., 1999; Howard et al., 2002; Haukka et al., 2003; Webb et al., 2005; Power et al., 2013). Not only are people with schizophrenia less likely to reproduce, but those that do have fewer offspring than healthy individuals (Nimgaonkar et al., 1997; MacCabe et al., 2009). In the case of affective psychosis, there is weaker evidence of reduced fertility (Howard et al., 2002; Murray et al., 2005), and some studies have found normal fertility (MacCabe et al., 2009).

With the exception of one small study looking at first episode psychosis (Hutchinson et al., 1999), previous research on fertility in psychoses has been carried out in people suffering from chronic psychosis. Therefore, it is very difficult to separate the impact of a predisposition to psychotic illnesses on fertility from the secondary effects of long-term hospitalisation, sexual dysfunction (Bobes et al., 2003), and neuroleptic-induced hyperprolactinaemia (Meaney and O'Keane, 2002).

We, therefore, sought to investigate pre-morbid fertility in a large, ethnically diverse sample of cases with a first episode of psychosis and

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population based controls drawn from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study (Morgan et al., 2006). In studying first episode cases at the point of illness onset, we hoped to reduce the impact of mediating effects mentioned above and capture data on pre-morbid fertility. We hypothesized that, as in previous studies, fertility would be reduced more significantly in people suffering from non-affective psychoses (Bundy et al., 2011) than in those with affective psychoses (MacCabe et al., 2009), and more in men than women (Vogel, 1979; Nanko and Moridaira, 1993; Nimgaonkar et al., 1997; McGrath et al., 1999; Howard et al., 2002; Haukka et al., 2003; Webb et al., 2005; Power et al., 2013). We also aimed to conduct exploratory analyses comparing variation in the extent of reduced fertility between different ethnic groups, in order to test whether belonging to an ethnic minority conferred some protection against low fertility, as observed by others (Hutchinson et al., 1999; Bhatia et al., 2004).

## 2. Methods

### 2.1. Sample: cases (see Kirkbride et al., 2006) for a detailed methodology)

The inclusion criteria for cases were: presence of a first episode of psychosis (F20–F29, F30–F33 (psychotic codings) in ICD-10 (WHO, 1992a)) within the time frame of the study; age 16–64; resident within defined catchment areas in south-east London and Nottingham and no previous contact with health services for the treatment of psychosis. Exclusion criteria were: evidence of psychotic symptoms precipitated by an organic cause or transient psychotic symptoms resulting from acute intoxication as defined by ICD-10.

Case finding procedures were based on those used by the World Health Organisation in its multi-country studies of schizophrenia (Jablensky et al., 1992). A team of researchers regularly checked all points of potential contact with secondary health services in the catchment areas. All potential cases were screened for inclusion using the Screening Schedule for Psychosis (Jablensky et al., 1992). Each person meeting the inclusion criteria was approached and informed consent sought. Case recruitment took place initially over two years. Recruitment of Black Caribbean cases was extended by 1 year to increase the size of this population in the case–control arm of the study.

### 2.2. Sample: controls

A random sample of population based control subjects, aged 16–64, was recruited. The sampling procedure was adapted from that used by the Office of Population and Census Statistics Psychiatric Morbidity Survey (Jenkins and Meltzer, 1995). The small users Postal Address File (PAFile) was used as the sampling frame. For each case ascertained, ten addresses within the same electoral ward were randomly generated from the PAFile. This ensured broad comparability between cases and controls by neighbourhood. Each address was contacted three times (morning, afternoon, and evening); if an eligible control was not recruited the procedure was repeated with another set of ten addresses. All adults in each household were invited to take part and where more than one occupant was willing to participate, a modified Kish grid was used to randomly select one member of the household. To ensure a sufficient number of Black Caribbean controls were recruited, we deliberately over-sampled this population by using a 'snowball' sampling technique. The Psychosis Screening Questionnaire (Bebbington and Nayani, 1995) was administered to all eligible controls; subjects who screened positive were excluded, and referred for further assessment and treatment if appropriate.

### 2.3. Data collection

#### 2.3.1. Sociodemographic data

We collected data relating to age, gender, fertility, and ethnicity using the Medical Research Council (MRC) Sociodemographic Schedule at the point of illness onset. The median duration of untreated illness in participants was 9.4 weeks. This period of illness could not have had an impact in fertility, thus allowing pre-morbid fertility to be assessed.

We calculated fertility as a binary variable (any offspring versus none) and two quantitative measures of fertility: mean number of children (MNC) and the mean number of children in those with at least one offspring (MNCO). The MNC measures whether fertility is reduced in the total sample and is useful in estimating the likely evolutionary selective pressure on rates of psychotic disorders. The MNCO is designed to restrict the analysis to people who are sexually active and biologically fertile. Both measures may also be useful in service provision planning for this population.

Ethnicity was based on subject self-ascription using 2001 UK Census categories. We categorised subjects into four ethnic groups: 1) White British; 2) Black Caribbean; 3) Black African; and 4) Other. The Black Caribbean sample included both subjects born in the Caribbean and subjects born in the UK to Caribbean parents. Likewise, the Black African sample included both subjects born in sub-Saharan Africa and born in the UK to sub-Saharan African parents. The 'Other' sample included people from India, Pakistan, and Bangladesh mainly, as well as people of mixed ethnicity.

#### 2.3.2. Diagnosis

Symptom data were collected using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992b). ICD-10 diagnoses were determined using the SCAN data on the basis of consensus meetings involving one of the AESOP study's Principal Investigators (RMM, PBJ, Julian Leff) and other members of the research team. Full details can be found in Kirkbride et al. (2006).

### 2.4. Analyses

All analyses were conducted using SPSS version 19 (SPSS, 2009) and STATA Version 9.2 (STATA, 2007). Statistical significance level for all analyses was set as $p = 0.05$. We weighted the data in the analyses to take account of the over-sampling of Black Caribbean controls. We assigned Black Caribbean controls a weight based on the proportion of Black Caribbeans in the populations of the two study catchment areas (estimated using 2001 Census data). All other controls and cases were assigned a weight of one.

We used logistic regression analyses to compare fertility as a binary variable between different groups (fertility rate). All analyses were adjusted for age alone (referred to as 'age-adjusted analyses' throughout the paper), or age, gender, ethnicity, religious background, education level, and history of a previous stable relationship ('adjusted analyses'). Fertility rate analyses were conducted for the full sample, and stratified by diagnosis, gender, and ethnicity. Likelihood ratio tests for age, ethnicity, and gender were carried out in the unadjusted analyses to test for interactions.

We used negative binomial regression and zero-truncated negative binomial regression analyses (Cameron and Trivedi, 1998; Hilbe, 2007; Coxe et al., 2009) to make case–control comparisons of the mean number of children (MNC) and the mean number of children in people with at least one child (MNCO), respectively. The negative binomial regression is a generalization of the Poisson regression. It has the same mean structure as a Poisson regression but has an extra parameter to model possible over-dispersion of the data (variance is greater than the mean). It is therefore more flexible than the standard Poisson regression which is typically used for the analysis of count data. However assessment of histograms of the number of children and preliminary Poisson regression analyses revealed over-dispersion in our study. We had to use a zero-truncated model with MNCO as we were comparing people with children, and therefore the lowest count was 1. Small numbers in subgroups meant that we were unable to stratify analyses of MNC and MNCO.