Modelling the Interplay between Childhood and Adult Adversity in Pathways to Psychosis:

Initial Evidence from the ÆSOP Study

Craig Morgan, PhD[*,1], **Ulrich Reininghaus, PhD**[*,1], **Paul Fearon, MRCPsych**[2], **Gerard Hutchinson, DM**[3], **Kevin Morgan, PhD**[4], **Paola Dazzan, MRCPsych**[2], **Jane Boydell, MRCPsych**[2], **James Kirkbride, PhD**[5], **Gillian A Doody, MRCPsych**[6], **Peter B Jones, FRCPsych**[5], **Robin M Murray, FRCPsych**[2], and **Tom Craig, FRCPsych**[1,2]

[1]NIHR Biomedical Research Centre, and Section of Social Psychiatry, Health Service and Population Research Department, Institute of Psychiatry, King's College, London, UK

[2]NIHR Biomedical Research Centre, and Psychosis Studies Department, Institute of Psychiatry, King's College, London, UK

[3]Psychiatry Unit, University of the West Indies, Trinidad

[4]Department of Psychology, Westminster University, London, UK

[5]Department of Psychiatry, University of Cambridge, Cambridge, UK

[6]Division of Psychiatry, University of Nottingham, Nottingham, UK

Abstract

Background—There is evidence that a range of socio-environmental exposures are associated with an increased risk of psychosis. However, despite the fact that such factors probably combine in complex ways to increase risk, the majority of studies have tended to consider each exposure separately. In light of this, we sought to extend previous analyses of data from the ÆSOP study on childhood and adult markers of disadvantage to examine how they combine to increase risk of psychosis, testing both mediation (path) models and synergistic effects.

Method—All patients with a first episode of psychosis who made contact with psychiatric services in defined catchment areas in London and Nottingham, UK (n = 390) and a series of community controls (n = 391) were included in the ÆSOP study. Data relating to clinical and

social variables, including parental separation and loss, education and adult disadvantage, were collected from cases and controls.

Results—There was evidence that the effect of separation from, but not death of, a parent in childhood on risk of psychosis was partially mediated through subsequent poor educational attainment (no qualifications), adult social disadvantage and, to a lesser degree, low self-esteem. In addition, there was strong evidence that separation from, but not death of, a parent combined synergistically with subsequent disadvantage to increase risk. These effects held for all ethnic groups in the sample.

Conclusions—Exposure to childhood and adult disadvantage may combine in complex ways to push some individuals along a predominantly socio-developmental pathway to psychosis.

Introduction

The study of specific exposures in relation to schizophrenia and other psychoses is essential to identify putative risk factors. However, this approach can only take us so far, and none of the risk factors identified to date are sufficient or necessary to cause psychosis. To more fully understand the aetiology of these disorders we need to investigate both how putative risk factors interact with each other and the mechanisms through which they impact on individuals in what are most probably complex webs of causation. This necessitates moving beyond efforts to isolate independent factors to consider causal paths and interactions.

A useful illustration of this is the recent accumulation of evidence linking various socio-environmental factors (e.g., abuse, disadvantage, migration and ethnicity) with both psychotic disorders and psychotic experiences in general population samples (Morgan *et al.*, 2008, van Dam *et al.*, 2012, Varese *et al.*, 2012). The studies that have implicated such factors have tended to consider each exposure separately, albeit with some notable exceptions (e.g., Bebbington *et al.*, 2011, van Os *et al.*, 2004, Zammit *et al.*, 2010b). This is despite the fact that social adversities and disadvantages tend to cluster in individuals, families and neighbourhoods and persist over time (Pantazis *et al.*, 2006), and most aetiological theories imply co-participation of a number of risk factors. For example, the proposition that social factors increase risk for psychosis via sensitisation of the dopaminergic system implies prolonged and cumulative exposure (Collip *et al.*, 2008, van Os *et al.*, 2010). In relation to understanding the high rates of psychosis in minority ethnic groups, where the current balance of evidence implicates socio-environmental factors (e.g., Cooper *et al.*, 2008, Morgan *et al.*, 2009, Reininghaus *et al.*, 2010, Veling *et al.*, 2011), we have proposed a theoretical model of a socio-developmental pathway to psychosis in which we hypothesise that the high prevalence of linked social adversities over time in certain minority groups accounts for the high rates (Morgan *et al.*, 2010). Such a model explicitly implicates a dynamic interplay between social factors over time and at different levels.

When considering how social and other factors may relate to each other in pathways to psychosis, there are a number of possibilities (Schwartz and Susser, 2006). First, some social factors may impact on risk indirectly by increasing likelihood of exposure to more proximal risk factors. For example, childhood adversity may link to psychosis, in part, via subsequent poor educational attainment (previously found to be associated with psychosis (Morgan et

al, 2008)) or via further adversity or via cognitive and affective mechanisms (e.g., self-esteem), such that childhood adversity is an early step on a causal path (i.e., a mediation model). A limited number of studies have examined mediation models linking, for example, exposure to trauma and psychological mechanisms such as self-esteem in paths to psychosis (Bebbington *et al.*, 2011, Fisher *et al.*, 2012). Second, social factors may combine synergistically (environment - environment interaction) to increase risk; that is, the impact of exposure to two factors may be greater than the sum of the individual effects of each alone (i.e., an interaction model). A larger number of studies have investigated synergistic effects for two environmental exposures (e.g., Clarke *et al.*, 2011, van Os *et al.*, 2004). To complicate this further, risk factors connected along a causal path (i.e., via mediation) may also interact (i.e., combine synergistically) (Hafeman, 2008). For example, the effect of childhood adversity may both predict subsequent adversity and interact with adult adversity (i.e., a mediated synergy model) (Hafeman and Schwartz, 2009). As far as we are aware, no studies have examined mediation and synergy in the same analyses in relation to psychosis. Assessment of these models (illustrated in Figure 1) is one way to expand the standard approach beyond identification of single risk factors. Framed in this way, theoretical propositions about how factors combine over time in neuro- or socio-developmental models of psychosis become empirically testable hypotheses.

In light of the above, we sought to extend previous analyses of data from the AESOP first-episode psychosis study on childhood and adult (Morgan *et al.*, 2007, 2008) markers of disadvantage to examine how they might combine to increase risk of psychosis. More specifically, we sought to test the hypotheses that childhood adversity both: (a) increases risk for psychosis in part via (i.e. is mediated through) poor education and adult disadvantage and self-esteem; and (b) interacts synergistically, on an additive scale, with poor education and adult disadvantage. Exposures and mediators were chosen on the basis of previous analyses demonstrating main effects of these variables on odds of psychosis (Morgan *et al.*, 2007, 2008). Our premise was that evidence supporting both hypotheses would be suggestive of mediated synergistic effects of these markers on risk of psychosis. In relation to ethnicity, we have previously noted that specific risk factors and mechanisms may contribute to higher rates of disorder in certain groups if they have a stronger effect or are more common. Having previously shown that markers of childhood and adult disadvantage are more common in black minority groups, we therefore further sought to test whether the effects hypothesised here, if evident, held for each of the main ethnic groups in our sample (white British, black Caribbean, black African). In this respect, our aim is to examine putative explanations of the increased incidence in black minority groups.

Method

AESOP is a multi-centre incidence and case-control study of first-episode psychosis. Full details of the methods are provided in previous reports (Morgan *et al.*, 2006).

Sample

The sample comprises cases with a first episode of psychosis and population-based controls. The inclusion criteria for cases were: age 16-64; resident within defined catchment areas in

south-east London and Nottingham, UK; presence of a first episode of psychosis within the time frame of the study; and no previous contact with health services for psychosis. Exclusion criteria were: evidence of psychotic symptoms precipitated by an organic cause; and transient psychotic symptoms resulting from acute intoxication as defined by ICD-10. Each patient meeting inclusion criteria was approached and informed consent sought. During the same period, a random sample of population-based controls with no history of psychosis aged 16-64 was recruited from the same catchment areas. The study received approval from the relevant local research ethics committees and all participants provided informed consent.

Data Collection

Detailed information on markers of adversity in childhood and adulthood was collected from cases and controls using the MRC Sociodemographic Schedule. The primary markers of childhood adversity used for the analyses presented in this paper were 1) separation from a parent before the age of 16 (with separation defined as not living in same household as one or both parents for one-year or more because of family breakdown); and 2) death of a parent before the age of 16 (Morgan *et al.*, 2007). With regard to current and long-term (i.e., one year prior to assessment) adult disadvantage and isolation we considered, where possible, five indicators: 1) unemployed; 2) living alone; 3) rented housing; 4) no relationship; and 5) limited social networks (Morgan *et al.*, 2008). To assess the impact of linked and cumulative disadvantage we created current and long-term indices by dichotomising each variable to indicate the presence or absence of an indicator, with a score of 1 for present (e.g. unemployed) and 0 for absent. This produced a potential range on the current index of 0 to 5 and on the long-term index of 0 to 3. (Long-term data were available for three markers only: unemployment, living alone, no relationship.) Poor educational achievement was operationalised as not having achieved any formal educational qualifications.

Self-esteem was assessed with the Rosenberg Self-Esteem Scale (Rosenberg, 1989). The questionnaire comprises 10-items (e.g., 'on the whole I am satisfied with myself') on a five-point scale. Total scores range from 10 to 50, with a higher score indicating more positive evaluations of the self.

Data on ethnicity, gender, and age were collected using the MRC Sociodemographic Schedule. Symptom data were collected using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992). ICD-10 diagnoses were determined by consensus. Premorbid IQ was estimated using the National Adult Reading Test and a parental history of psychosis was established using the Family Interview for Genetic Studies.

Data analysis

To test our hypotheses we first examined whether there was evidence that the effects of a) parental separation and b) parental death before the age of 16 on case-control status were mediated through poor education and adult disadvantage and self-esteem using multiple mediation analysis (MacKinnon, 2008). In line with Preacher & Hayes (2008), the total effect of parental separation (and of parental death) on case-control status was apportioned into a direct effect and mediating or, synonymously, indirect effects through poor education

and adult disadvantage and self-esteem. The total indirect effect was computed as the sum of specific indirect effects. Logit coefficients and odds ratios for total and specific indirect effects of parental separation and parental death through the hypothesised mediators on case-control status were estimated using maximum likelihood (ML) estimation in MPlus, Version 6.1 (Muthen and Muthen, 1998-2012). All mediation analyses were repeated using the robust weighted least squares means and variance adjusted estimator (WLSMV) to compute probit coefficients, as this approach provides more accurate estimates of direct, indirect, and total effects and allows for use of bias-corrected bootstrapping.[29, 30] Findings from these analyses (see supplementary materials) were in line with those produced using logit coefficients and odds ratios, which are presented in preference in the main body of the paper because they are more readily interpretable. Data were assumed to be missing at random, which allowed for inclusion of the full sample using WLSMV and ML estimators.

Next, we examined whether there was evidence that childhood adversity (i.e., a) separation from a parent; b) death of a parent) combined synergistically with poor education and/or adult disadvantage by testing for interaction on an additive scale (i.e., for departure from additivity) using interaction contrast ratios (ICR), as described by Schwartz et al[23]. Under the assumption that when the disorder is rare odds ratios approximate risk ratios, this approach uses odds ratios to estimate the relative excess risk due to interaction (i.e., ICR = $OR_{exposure\ A\ \&\ exposure\ B}$ - $OR_{exposure\ A\ only}$ - $OR_{exposure\ B\ only}$ +1). In this model, deviation from additivity (i.e., interaction) is indexed by an ICR greater than 0. Confidence intervals and p-values for ICRs were generated using the nlcom procedure in STATA.

Analyses were conducted using STATA Version 12 and MPlus Version 6.1.

Results

A total of 390 cases and 391 controls were assessed in the south-east London and Nottingham sites of the ÆSOP study over a 3-year period. Basic socio-demographic characteristics and the main social exposures and mediators by case-control status, and the distribution of diagnoses among cases, are shown in Table 1.

Previous Findings

In our previous analyses, we demonstrated strong and independent associations between psychosis and both a) separation from a parent (Adj. OR 2.45) and death of a parent (Adj. OR 3.06) and b) all current and long term indicators of social disadvantage (Adj. ORs ranged from 2.11 to 7.50) (Morgan *et al.*, 2008, Morgan *et al.*, 2007). When indicators of social disadvantage were combined to form indices, there was clear evidence of linear relationships, such that as the number of indicators present (current and long-term) increased the odds of psychosis increased (Morgan *et al.*, 2008). In addition, compared with controls, cases were almost 3 times more likely to have no formal qualifications (Adj. OR 2.92, 95% CI 1.98-4.30).

Mediation (1) Parental Separation, Education and Adult Disadvantage

To assess pathways from childhood adversity to psychosis via education and adult disadvantage, estimates of the total effects of parental separation and of parental death on

odds of psychosis were parsed into direct (i.e., unmediated) and indirect (total and specific) effects using multiple mediation analyses, as detailed above.

Beginning with separation, both unadjusted direct (OR 2.42, 95% CI 1.71-3.42) and total indirect (OR 2.46, 95% CI 1.60-3.80) effects of separation on case-control status were statistically significant at conventional 5% levels, indicating strong evidence for partial mediation via education and current disadvantage. These findings remained when adjusted for age, gender, ethnicity, study centre, and parental history of psychosis (direct effect: Adj. OR 1.61, 95% CI 1.09-2.40; total indirect effect: Adj. OR 4.35, 95% CI 2.11-8.95) (Table 2 and Figure 2; see Supplementary Table 1 for probit estimates). The total indirect effect of separation, after adjustment, accounted for around 75% of the total effect of separation from a parent on case-control status. In other words, a substantial proportion of the impact of separation on psychosis was via pathways through poor educational attainment (no qualifications) and adult disadvantage. Second, when specific indirect effects were scrutinised there was evidence for pathways from separation to psychosis via no qualifications alone (Adj. OR 2.38, 95% CI 1.34-4.20), via adult disadvantage alone (Adj. OR 1.16, 95% CI 0.99-1.37), and via no qualifications and adult disadvantage (Adj. OR 1.57, 95% CI 1.20-2.06). When stratified by ethnic group, the effects were very similar for the white British and black Caribbean groups; for the black African group the indirect effects did not hold, but confidence intervals were wide which suggests this may reflect loss of power (see Table 2 footnote). Further, when we repeated the above analyses using (a) our index of long-term disadvantage (Supplementary Table 2a and 2b) and (b) a sample of cases restricted to those with a very short DUP (1 month or less) (Supplementary Table 3a and 3b), very similar findings emerged, i.e. strong evidence for partial mediation via poor education and adult disadvantage.

Mediation (2) Self-Esteem

Further elaborating the model, in a sub-sample of 240 cases and 295 controls on whom data were available on current self-esteem, we examined whether the effects of separation and adult disadvantage were mediated via self-esteem at entry into the study. First, in this sub-sample the patterns of association and mediation described above broadly held. Second, there was weak evidence (Unadj. OR 1.02, 95% CI 1.00-1.05 p = 0.096) for a pathway from separation to psychosis via education, disadvantage and low self-esteem (Figure 3 and Supplementary Tables 4a and 4b).

Mediation (3) Accounting for Premorbid IQ

To assess whether our findings in relation to mediation via education and disadvantage could be accounted for by premorbid cognitive deficits, we repeated the relevant analyses above in a restricted sample with data on estimated pre-morbid IQ (n = 457) (Supplementary Tables 5a and 5b). To begin with, in this restricted sample, the strength of unadjusted and adjusted direct and indirect effects of parental separation were similar to those shown in Table 2. When these effects were further adjusted for premorbid IQ both direct and total indirect effects were attenuated but remained significant at conventional levels. All specific indirect effects were attenuated and only a pathway through poor education and current disadvantage (p = 0.071) was close to the standard 5% level of statistical significance.

Mediation (4) Parental Death

With regard to parental death, the proportion in the sample reporting loss of a parent during childhood was too small to allow for stable estimates of specific indirect effects. Unadjusted findings for direct and total indirect effects were broadly similar in magnitude to those for separation, but only reached conventional levels of statistical significance for direct effects (see Table 2). The direct effect for parental death remained robust to adjustment for age, gender, ethnicity, study centre, and parental history of psychosis (Table 2), and premorbid IQ (Supplementary Table 4).

Synergistic Effects

Following on from our analyses of mediation, we next examined evidence for synergistic effects of parental separation and both poor education (i.e., no qualifications) and adult disadvantage on risk of psychosis. For these analyses, our index of disadvantage was dichotomised into those exposed to no markers and those exposed to one or more. Beginning with separation and poor education, there was only suggestive evidence of departure from additivity: the adjusted odds ratio for those exposed to separation only was 1.46 (95% CI 0.95-2.25), for those exposed to poor education only it was 2.27 (95% CI 1.39-3.71), and for those exposed to both it was 5.78 (3.04-10.98) (ICR 3.05, 95% CI -0.62-6.72, $p = 0.103$; see Figure 4a). Turning to separation and disadvantage, there was strong evidence of departure from additivity: the adjusted odds ratio for those exposed to separation only was 0.89 (95% CI 0.27-2.95), for those exposed to markers of disadvantage only it was 3.95 (95% CI 2.24-6.97), and for those exposed to both it was 8.14 (95% CI 4.26-15.55) (ICR 4.30, 95% CI 0.66-7.94, $p = 0.021$; see Figure 4b). These effects were broadly similar across the three main ethnic groups (data not shown; available on request).

When we repeated these analyses restricted to the sample with data on premorbid IQ and further adjusted analyses for premorbid IQ, the interaction between separation and disadvantage was attenuated (ICR 2.83, 95% CI -0.79-6.45, $p = 0.126$). This may, however, largely reflect a loss of power, as the estimated ICR remained notably above zero and confidence intervals are wide.

There was no evidence for additive interaction between parental death and either education or disadvantage (data not shown; available on request).

Discussion

Building on previous analyses of the AESOP sample, we sought to move beyond identification of single environmental risk factors to examine whether markers of childhood adversity combine with other socio-environmental factors to increase risk of psychosis by testing path (mediation) models and synergistic effects. Three primary findings emerged: (1) there was strong evidence that the effect of separation from (but not death of) a parent on risk of psychosis was partially mediated through subsequent poor educational attainment and social disadvantage and, more tentatively, low self-esteem; (2) there was strong evidence that separation (but not death) interacted synergistically, on an additive scale, with disadvantage to increase risk; and (3) there was no evidence that the mediation or interaction

effects varied by ethnicity. The evidence for both mediated and synergistic effects is suggestive of mediated synergy (i.e., of separation from a parent both increasing likelihood of, and interacting with, subsequent social disadvantage). It is notable, moreover, that similar effects were not observed for loss of a parent during childhood. This, of course, may be due to a lack of power given parental loss is relatively rare and therefore needs to be interpreted cautiously. This noted, it raises the possibility that specific factors may have specific effects and operate through different paths and mechanisms, and this merits further consideration in future research.

Methodological Limitations

Data for this study were collected retrospectively at a single time point, which inevitably limits the inferences that can be drawn regarding causal pathways. We did, however, select variables that are temporally sequential such that it is reasonable to assume in most cases that parental separation prior to age 16 years preceded educational level (i.e., no qualifications on leaving school at 16 years or subsequently), which in turn preceded disadvantage and self-esteem (determined at point of assessment, i.e. after age 16 years). Perhaps more problematically, as disadvantage and self-esteem were assessed after onset of disorder, we cannot determine the direction of causation between these and psychosis. However, we have shown in previous analyses that associations between case-control status and markers of disadvantage held when the sample was restricted to those with a very short DUP (< 1 month) and when long-term indicators of social disadvantage were considered, which suggests high levels of disadvantage in the case sample are not simply a consequence of disorder (Morgan *et al.*, 2008). In a more recent study, we replicated these findings and further showed that markers of disadvantage were present 5 years prior to onset (Stilo *et al.*, 2012). Similarly, in the analyses presented in this paper, when we both restricted the sample to those with a short DUP and repeated analyses using the long-term index of social disadvantage the findings were the same.

We were able to adjust for a parental history of psychosis and, in a sub-sample, for estimated premorbid IQ, and the findings remained largely robust. Parental history, however, is a limited proxy for genetic risk and we cannot entirely rule out the possibility that some of the observed effects are a consequence of underlying genetic susceptibility. Polygenic risk scores may provide more useful summaries of total genetic risk that can be employed in future studies (Purcell *et al.*, 2009). In addition, we cannot rule out confounding by unmeasured factors such as substance use. What this indicates is that the models we have tested are inevitably partial.

Our finding of evidence for synergistic effects on an additive scale should be interpreted with caution. As has been discussed in relation to gene - environment interactions, models are scale dependent (Zammit *et al.*, 2010a). Recent critiques of interaction analyses, particularly of additive models, emphasise the need to determine analyses and scale for interaction a priori, especially given the high probability of Type I error (Zammit *et al.*, 2010a). Our decision to model interactions on an additive scale was made because, within a minimum sufficient causes framework, additive models provide the best representation of synergy (Rothman *et al.*, 1980, Schwartz, 2006). In addition, as others have noted,

multiplicative models are more complex and prone to error and, from a public health perspective, they are not as informative as additive models, which provide more readily interpretable information on the combined impact of two risk factors over and above what would be expected from each one alone (Kendler and Gardner, 2010).

It further bears noting that our key exposure variables are perhaps most usefully considered risk indicators that probably index exposure, in some but not all, to risk factors that are more common among those who are separated and who are unemployed, living alone and so on. That there are multiple effects of separation on risk further hints at this. The meaning and impact of separation, for example, is probably diffuse; indeed, our findings suggest separation indicate exposure to processes that impact on risk of psychosis both directly (e.g., disrupted attachments, intra-familial conflict and neglect), which in turn may combine synergistically with subsequent exposures, and indirectly via other variables, e.g. education and subsequent disadvantage. What is more, this may explain why the same exposures are often associated with a heterogeneous range of outcomes; that is, specificity may lie in the particular paths that follow initial exposures, and this points strongly to a need for more detailed and robust measures of social exposures.

Interplay between Social Factors

The above limitations noted, the analyses reported here both illustrate how multiple (social) risk factors can be simultaneously modelled to provide clues on how they combine in developmental trajectories to psychosis and provide initial evidence in relation to childhood adversity, subsequent disadvantage and (tentatively) self-esteem.

Our analyses tie in with a developing literature considering how social and non-social environmental factors combine and interact over time to increase risk of psychosis. There is, for example, increasing evidence for cross-level social environment - environment interactions, such that the effects of individual-level exposures (e.g., being single) often depend on area-level exposures (e.g., living in area with few single people) (van Os *et al.*, 2000). In relation to non-social environmental factors, Clarke et al (2011) found evidence for interaction between obstetric complications and delayed developmental milestones in risk for schizophrenia using data from population records in Helsinki, Finland. With regard to causal paths, Bebbington et al (2011) found evidence consistent with a pathway from childhood sexual abuse to psychosis via anxiety and depression in their analyses of data from the 2007 Adult Psychiatric Morbidity Survey in England (n in analysis = 7353). More recently, Fisher et al (2012) in analyses of data from the ALSPAC birth cohort (n in analyses = 6692), found that the effects of harsh parenting and bullying prior to 8.5 years old on risk of psychotic experiences at age 13 years were fully or partially mediated by anxiety, depressive symptoms, external locus of control and low self-esteem. Our findings are consistent with and add to this developing literature and further extend it by modelling paths and interactions within the same analyses. There is, however, some way to go before our models capture the complexity that undoubtedly underlies developmental trajectories to psychosis. In this respect, models of the environmental antecedents of psychosis are currently less well developed and empirically supported than those for other disorders (e.g.,

depression (Brown *et al.*, 2007)); this wider literature points a way forward for studies of psychosis.

In relation to socio-environmental factors, it is important to note that there is now evidence for plausible mechanisms that may account for how external social experiences impact on individuals in such a way as to increase risk of psychosis (e.g., via effects of stress on dopamine (Howes and Kapur, 2009), the HPA axis (Mondelli *et al.*, 2010), neural function (Lederbogen *et al.*, 2011) and cognition and affect (Fowler *et al.*, 2012)). These findings, in turn, validate the importance of environmental factors and provide further impetus to research on how such factors combine and interact with each other to increase risk of disorder.

A Sociodevelopmental Pathway?

Social disadvantage, broadly defined, frequently persists over time and is often associated with poor outcomes in a number of domains (e.g., education, health, housing, etc.); these poor outcomes in turn further entrench and amplify disadvantage, creating for many a vicious downward cycle of poverty and exclusion (Pantazis *et al.*, 2006). Given this, it is plausible that one pathway from adversity in childhood to psychosis is via persistent exposure to disadvantage in adulthood and consequent low self-esteem. With this in mind, we have previously proposed a predominantly socio-developmental pathway to psychosis, in which, for some, adverse social experiences in childhood link to psychosis via and in interaction with further cumulative stressors in adulthood (and indeed other factors, e.g., substance use) (Morgan *et al.*, 2010). The analyses presented here are, put cautiously, consistent with this. Further, this model was proposed primarily to explain the high rates of psychosis observed in some minority ethnic populations, particularly the black Caribbean in the UK, in which there are very high levels of social disadvantage across the life course. The data are, again put cautiously, consistent with this (i.e., similar effect sizes among populations, higher prevalence of exposure in one population).

Unraveling these complex connections is of potential public health importance. Put simply, if initial disadvantage in childhood is not followed by later disadvantage, the overall effect of, say, separation from a parent on risk may be reduced, a possibility with tangible public health implications. Related to this, there is emerging interest in the role of protective factors and resilience in mitigating the effect of social adversities on risk of psychosis (Gayer-Anderson and Morgan, 2012). It may be, then, that by identifying how social (and other) factors that may be amendable to change connect over time in complex causal webs, we can gain further traction on when and how to intervene to reduce risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Bebbington P, Jonas S, Kuipers E, King M, Cooper C, Brugha T, Meltzer H, McManus S, Jenkins R. Childhood sexual abuse and psychosis: data from a cross-sectional national psychiatric survey in England. Br J Psychiatry. 2011; 199:29–37. [PubMed: 21508437]

Brown GW, Craig TK, Harris TO, Handley RV, Harvey AL, Serido J. Child-specific and family-wide risk factors using the retrospective Childhood Experience of Care & Abuse (CECA) instrument: a life-course study of adult chronic depression - 3. J Affect Disord. 2007; 103:225–36. [PubMed: 17689666]

Clarke MC, Tanskanen A, Huttunen M, Leon DA, Murray RM, Jones PB, Cannon M. Increased risk of schizophrenia from additive interaction between infant motor developmental delay and obstetric complications: evidence from a population-based longitudinal study. Am J Psychiatry. 2011; 168:1295–302. [PubMed: 21890789]

Collip D, Myin-Germeys I, Van Os J. Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? Schizophr Bull. 2008; 34:220–5. [PubMed: 18203757]

Cooper C, Morgan C, Byrne M, Dazzan P, Morgan K, Hutchinson G, Doody G, Harrison G, Leff J, Jones P, Ismail K, Murray R, Bebbington P, Fearon P. Perceptions of disadvantage, ethnicity and psychosis: results from the ÆSOP study. British Journal of Psychiatry. 2008; 192:185–190. [PubMed: 18310577]

Fisher H, Schreier A, Zammit S, Maughan B, Munafo MR, Lewis G, Wolke D. Pathways between childhood victimisation and psychosis-like symptoms in the ALSPAC birth cohort. Schizophrenia Bulletin. 2012

Fowler D, Hodgekins J, Garety P, Freeman D, Kuipers E, Dunn G, Smith B, P EB. Negative Cognition, Depressed Mood, and Paranoia: A Longitudinal Pathway Analysis Using Structural Equation Modeling. Schizophr Bull. 2012

Gayer-Anderson C, Morgan C. Social networks, support and early psychosis: a systematic review. Epidemiol Psychiatr Sci. 2012:1–16.

Hafeman DM. A sufficient cause based approach to the assessment of mediation. Eur J Epidemiol. 2008; 23:711–21. [PubMed: 18798000]

Hafeman DM, Schwartz S. Opening the Black Box: a motivation for the assessment of mediation. Int J Epidemiol. 2009; 38:838–45. [PubMed: 19261660]

Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 2009; 35:549–62. [PubMed: 19325164]

Kendler KS, Gardner CO. Interpretation of interactions: guide for the perplexed. Br J Psychiatry. 2010; 197:170–1. [PubMed: 20807958]

Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, Wust S, Pruessner JC, Rietschel M, Deuschle M, Meyer-Lindenberg A. City living and urban upbringing affect neural social stress processing in humans. Nature. 2011; 474:498–501. [PubMed: 21697947]

MacKinnon, D. Introduction to Statistical Mediation Analysis. Lawrence Erlbaum Associates; New York: 2008.

Mondelli V, Dazzan P, Hepgul N, Di Forti M, Aas M, D'Albenzio A, Di Nicola M, Fisher H, Handley R, Marques TR, Morgan C, Navari S, Taylor H, Papadopoulos A, Aitchison KJ, Murray RM, Pariante CM. Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment. Schizophr Res. 2010; 116:234–42. [PubMed: 19751968]

Morgan C, Charalambides M, Hutchinson G, Murray RM. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. Schizophr Bull. 2010; 36:655–64. [PubMed: 20513653]

Morgan C, Dazzan P, Morgan K, Jones P, Harrison G, Leff J, Murray R, Fearon P. First episode psychosis and ethnicity: initial findings from the AESOP study. World Psychiatry. 2006; 5:40–6. [PubMed: 16757995]

Morgan C, Fisher H, Hutchinson G, Kirkbride J, Craig TK, Morgan K, Dazzan P, Boydell J, Doody GA, Jones PB, Murray RM, Leff J, Fearon P. Ethnicity, social disadvantage and psychotic-like experiences in a healthy population based sample. Acta Psychiatr Scand. 2009; 119:226–35. [PubMed: 19053965]

Morgan C, Kirkbride J, Hutchinson G, Craig T, Morgan K, Dazzan P, Boydell J, Doody GA, Jones PB, Murray RM, Leff J, Fearon P. Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. Psychol Med. 2008; 38:1701–15. [PubMed: 19000327]

Morgan C, Kirkbride J, Leff J, Craig T, Hutchinson G, McKenzie K, Morgan K, Dazzan P, Doody GA, Jones P, Murray R, Fearon P. Parental separation, loss and psychosis in different ethnic groups: a case-control study. Psychol Med. 2007; 37:495–503. [PubMed: 17094816]

Muthen, LK.; Muthen, B. Mplus Version 6.1. Los Angeles, CA: 1998-2012.

Pantazis, C.; Gordon, D.; Levitas, R., editors. Poverty and Social Exclusion in Britain: The Millenium Survey. The Policy Press; Bristol: 2006.

Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008; 40:879–91. [PubMed: 18697684]

Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; 460:748–52. [PubMed: 19571811]

Reininghaus U, Craig TK, Fisher HL, Hutchinson G, Fearon P, Morgan K, Dazzan P, Doody GA, Jones PB, Murray RM, Morgan C. Ethnic identity, perceptions of disadvantage, and psychosis: findings from the AESOP study. Schizophr Res. 2010; 124:43–8. [PubMed: 20855184]

Rosenberg, M. Society and the Adolescent Self-Image. Middletown, CT; Wesleyan University Press: 1989.

Rothman KJ, Greenland S, Walker AM. Concepts of interaction. Am J Epidemiol. 1980; 112:467–70. [PubMed: 7424895]

Schwartz, S. Modern epidemiologic approaches to interaction: applications to studies of genetic interactions. In: Hernandez, LM.; Blazer, DG., editors. In Genes, Behaviour and the Social Environment: Moving Beyond the Nature/Nurture Debate. National Academies Press; Washington DC, USA: 2006. p. 310-337.

Schwartz, S.; Susser, E. Relationships among causes. In Psychiatric Epidemiology: Searching for the Causes of Mental Disorders. In: Susser, E.; Schwartz, S.; Morabia, A.; Bromet, EJ., editors. Oxford University Press; Oxford: 2006. p. 62-74.

Stilo S, Di Forti M, Mondelli V, Falcone AM, Russo M, O Connor J, Palmer E, Paparelli A, Kolliakou A, Sirianni M, Taylor H, Handley R, Dazzan P, Pariante C, Marques T, Zoccali R, David AS, Murray R, Morgan C. Social disadvantage: cause or consequence of impending psychosis? Schizophrenia Bulletin. 2012

van Dam DS, van der Ven E, Velthorst E, Selten JP, Morgan C, de Haan L. Childhood bullying and the association with psychosis in non-clinical and clinical samples: a review and meta-analysis. Psychol Med. 2012:1–12.

van Os J, Driessen G, Gunther N, Delespaul P. Neighbourhood variation in incidence of schizophrenia. Evidence for person-environment interaction. Br J Psychiatry. 2000; 176:243–8. [PubMed: 10755071]

van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature. 2010; 468:203–12. [PubMed: 21068828]

van Os J, Pedersen CB, Mortensen PB. Confirmation of synergy between urbanicity and familial liability in the causation of psychosis. Am J Psychiatry. 2004; 161:2312–4. [PubMed: 15569906]

Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, Read J, van Os J, Bentall RP. Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies. Schizophr Bull. 2012; 38:661–71. [PubMed: 22461484]

Veling W, Hoek HW, Selten JP, Susser E. Age at migration and future risk of psychotic disorders among immigrants in the Netherlands: a 7-year incidence study. Am J Psychiatry. 2011; 168:1278–85. [PubMed: 22193672]

WHO. Schedules for Clinical Assessment in Neuropsychiatry. World Health Organisation; Geneva: 1992.

Zammit S, Lewis G, Dalman C, Allebeck P. Examining interactions between risk factors for psychosis. Br J Psychiatry. 2010a; 197:207–11. [PubMed: 20807965]

Zammit S, Lewis G, Rasbash J, Dalman C, Gustafsson JE, Allebeck P. Individuals, schools, and neighborhood: a multilevel longitudinal study of variation in incidence of psychotic disorders. Arch Gen Psychiatry. 2010b; 67:914–22. [PubMed: 20819985]

adult adversity

childhood adversity

psychosis
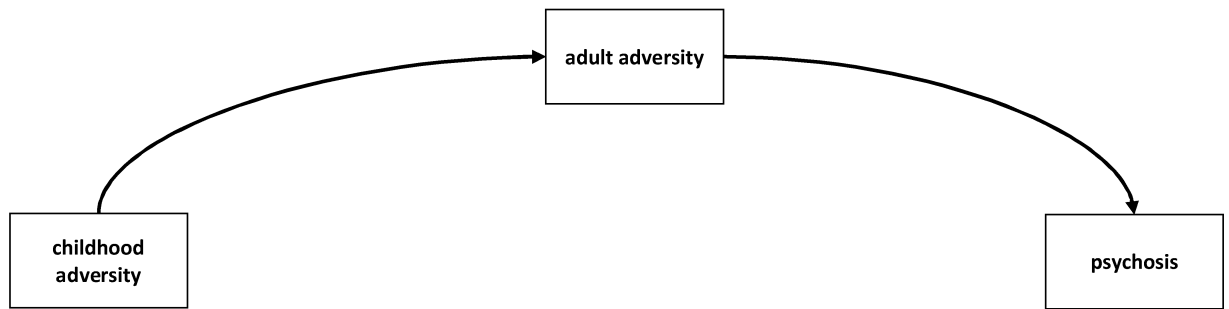
(a) **Mediation.** The effect of the primary exposure (childhood adversity) is via its impact on likelihood of exposure to a more proximal exposure (adult adversity).

adult adversity

childhood adversity

psychosis
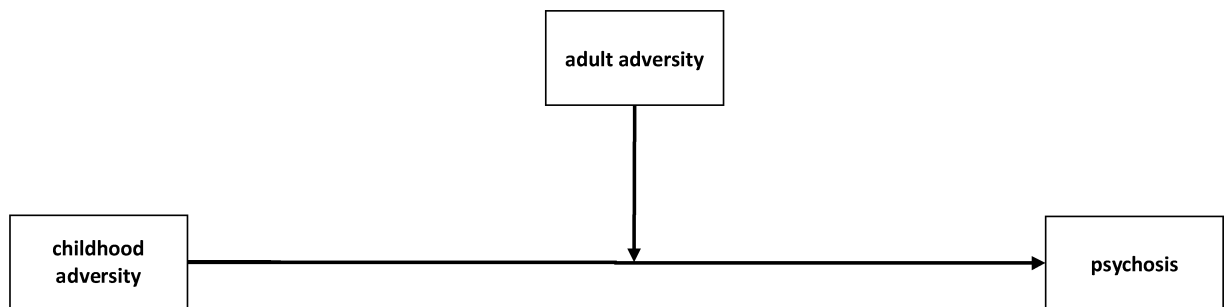
(b) **Synergy (interaction, effect modification).** The effect of the primary exposure (childhood adversity) combines with (or depends on) another exposure (adult adversity) to increase risk.

adult adversity

childhood adversity
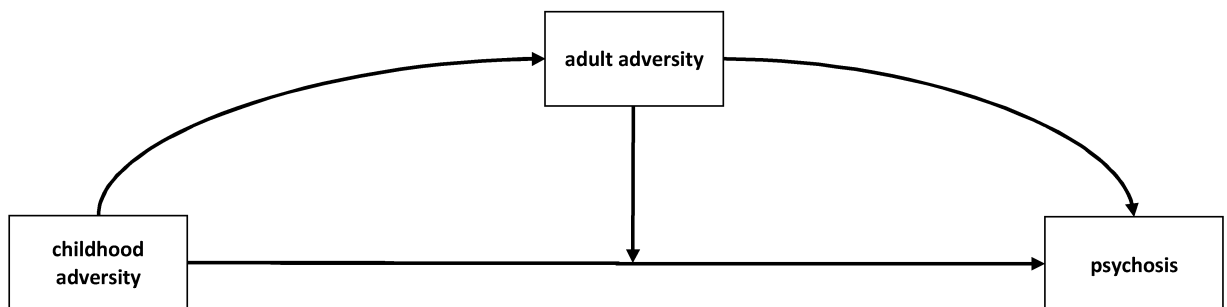
psychosis

(c) **Mediated synergy.** The primary exposure (childhood adversity) may both (i) (partly) impact on psychosis via a more proximal exposure (adult adversity) and (ii) interact with that exposure (adult adversity) to increase risk of psychosis.

Figure 1.
Models of mediation, synergy and mediated synergy.
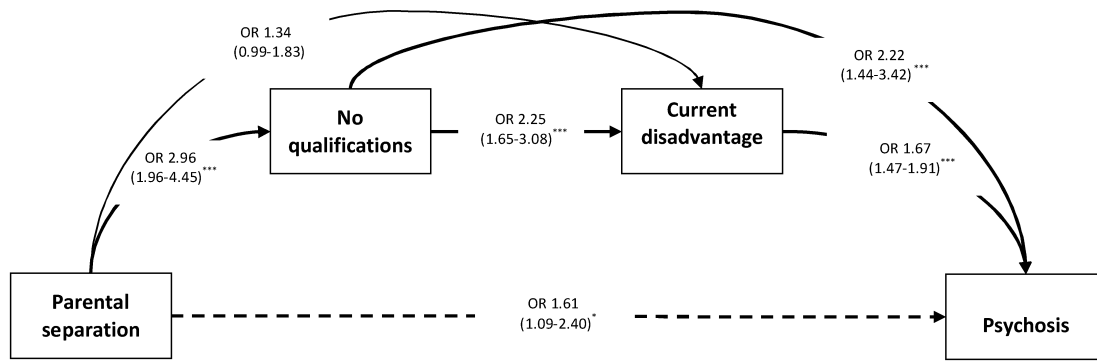
Notation: ☐ observed variables; ⟶ significant indirect effect; ┈▶ non-significant indirect effect; ┄▶ direct effect; * P < .05 ; ** P < .01; *** P < .001.

† Parental separation: Direct effect   Adj. OR 1.61   (1.09-2.40)
                         Total indirect effect   Adj. OR 4.35   (2.11-8.95)
                         Specific indirect effects
                             No qualifications   Adj. OR 2.38   (1.34-4.20)
                             Current disadvantage   Adj. OR 1.16   (0.99-1.37)
                             No qualifications – Current disadvantage   Adj. OR 1.57   (1.20-2.06)
                         Total effect   Adj. OR 7.02   (3.21-15.35)

‡ **Explanatory Note** Compared with controls, cases were 2.38 times more likely to have been separated from a parent and go on to have no qualifications. Further, cases were 1.16 times more likely to have been separated from a parent and, in turn, experience social disadvantage. Cases were 1.57 times more likely to have been separated from a parent, followed by no qualifications and, then, social disadvantage. Overall, compared with controls, cases were 4.35 times more likely to experience one of these three pathways.
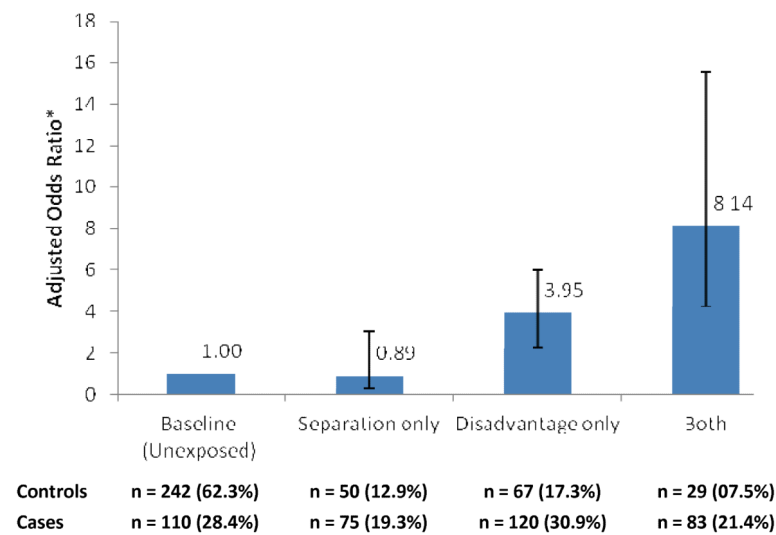
Figure 2.

Path diagram of odds ratios (95% CI) of parental separation, educational level, and current social disadvantage on case-control status adjusted for age, gender, ethnicity, study centre, and parental history of psychosis (n = 781, 65 free parameters). †‡
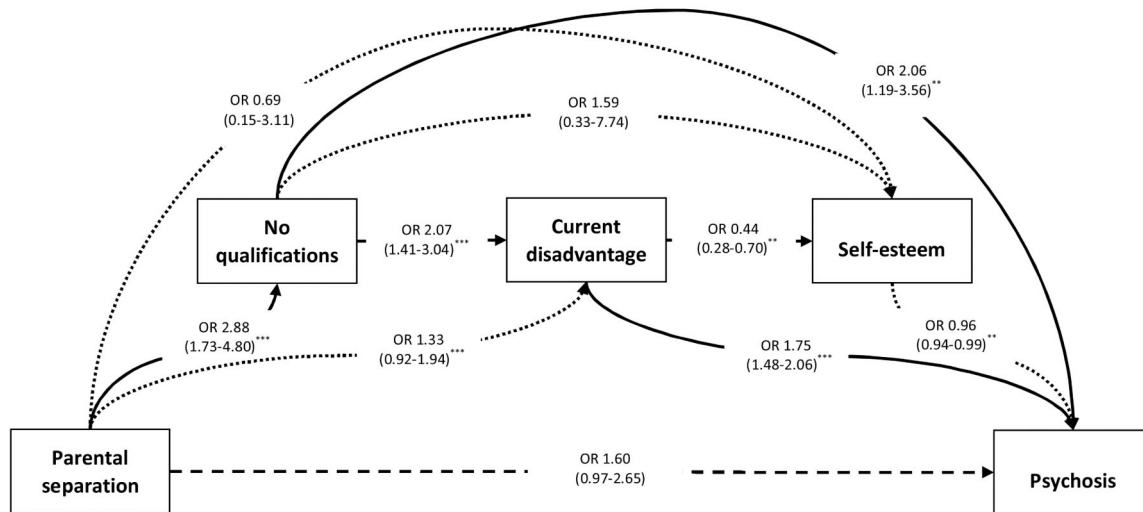
Notation: ☐ observed variables; ➝ significant indirect effect; ⋯➤ non-significant indirect effect; ---➤ direct effect; * P < .05 ; ** P < .01; *** P < .001.

† Parental separation:	Direct effect	Adj. OR 1.60	(0.97-2.65)
	Total indirect effect	Adj. OR 3.99	(1.65-9.65)
	Specific indirect effects		
	No qualifications	Adj. OR 2.15	(1.08-4.26)
	Current disadvantage	Adj. OR 1.17	(0.95-1.45)
	Self-esteem	Adj. OR 1.01	(0.96-1.08)
	No qualifications – Current disadvantage	Adj. OR 1.54	(1.10-2.14)
	No qualifications – Self-esteem	Adj. OR 0.98	(0.92-1.05)
	Current disadvantage – Self-esteem	Adj. OR 1.01	(0.99-1.02)
	No qual – Curr Disadvant – Self-esteem	Adj. OR 1.02	(1.00-1.05)
	Total effect	Adj. OR 6.41	(2.44-16.86)

‡ **Explanatory Note** Compared with controls, cases were 2.15 times more likely to have been separated from a parent and go on to have no qualifications. Further, cases were 1.54 times more likely to have been separated from a parent, followed by no qualifications and, in turn, experience social disadvantage. A trend (p = 0.096) was observed for the indirect effects of parental separation to poor education to current disadvantage to self-esteem to psychosis.

Figure 3.
Path diagram of odds ratios (95% CI) of parental separation, educational level, current social disadvantage, and self-esteem on case-control status adjusted for age, gender, ethnicity, study centre, and parental history of psychosis (n = 781, 65 free parameters). †‡

a) Separation and education

	Baseline (Unexposed)	Separation only	Poor education only	Both
Controls	n = 255 (65.7%)	n = 62 (16.0%)	n = 54 (13.9%)	n = 17 (04.4%)
Cases	n = 172 (44.3%)	n = 92 (23.7%)	n = 58 (15.0%)	n = 66 (17.0%)
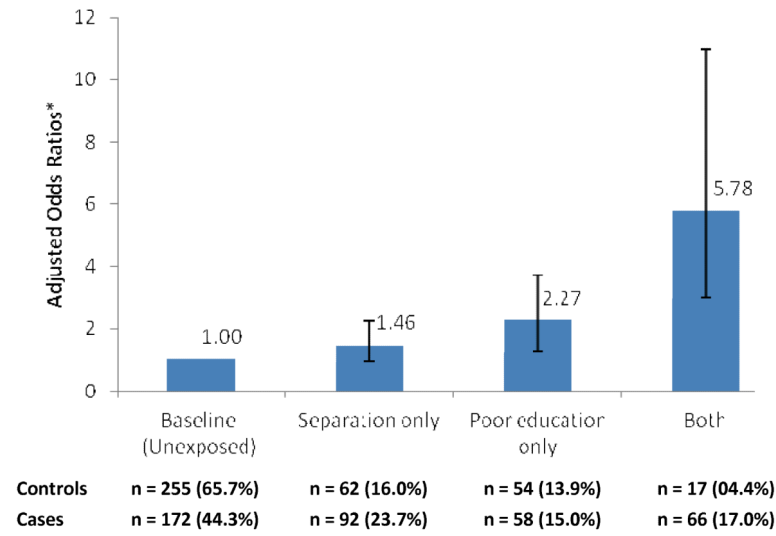
Interaction Contrast Ratio 3.05, 95% CI -0.62-6.72, p = 0.103

b) Separation and disadvantage

	Baseline (Unexposed)	Separation only	Disadvantage only	Both
Controls	n = 242 (62.3%)	n = 50 (12.9%)	n = 67 (17.3%)	n = 29 (07.5%)
Cases	n = 110 (28.4%)	n = 75 (19.3%)	n = 120 (30.9%)	n = 83 (21.4%)

Interaction Contrast Ratio ICR 4.30, 95% CI 0.66-7.94, p = 0.021

* Odds ratios adjusted for age, gender, ethnicity, study centre, and parental history of psychosis

Figure 4.
Additive interactions between separation from a parent and poor education and adult disadvantage.

Table 1

Basic sociodemographic and diagnostic characteristics by case-control status.

	Controls (n = 391)		Cases (n = 390)		t	df	p
Age							
Mean	37.3		30.5		8.20	779	<0.001
Sd	12.5		10.8				
Self-esteem[*]							
Mean	39.2		36.2		4.48	533	<0.001
Sd	7.6		7.8				
	n (%)		n (%)		χ^2	df	p
Sex							
Male	161	(41.2)	218	(55.9)	16.94	1	<0.001
Female	230	(58.8)	172	(44.1)			
Ethnicity							
White British	240	(61.4)	177	(45.4)	35.21	5	<0.001
Other White	42	(10.7)	28	(7.2)			
African-Caribbean	74	(18.9)	107	(27.4)			
Black African	22	(5.6)	43	(11.0)			
Asian (all)	8	(2.1)	22	(5.6)			
Other	5	(1.3)	13	(3.3)			
Parental separation and loss							
None	297	(76.0)	200	(51.3)	51.4	2	<0.001
Separation	80	(20.4)	160	(41.0)			
Loss of parent	14	(3.6)	30	(7.7)			
Current disadvantage index							
0	121	(21.2)	24	(6.2)	127.8	5	<0.001
1	99	(25.5)	62	(16.0)			
2	72	(18.6)	99	(25.5)			
3	67	(17.3)	107	(27.6)			
4	25	(6.4)	57	(14.7)			
5	4	(1.0)	39	(10.1)			
Education							
No qualifications	71	(18.3)	124	(32.0)	19.2	1	<0.001
Any qualifications	317	(81.7)	264	(68.0)			
Parental history of psychosis							
No	384	(98.2)	312	85.5	41.9	1	<0.001
Yes	7	(1.79)	53	14.5			
Diagnosis							
Non-affective psychosis	-	-	263	(67.4)	-	-	-
Affective psychosis	-	-	127	(32.6)	-	-	-

[*] sample size n = 535 (240 cases, 295 controls)

Table 2

Total, direct, total indirect, and specific indirect effects (odds ratios) of parental separation, educational level, and current social disadvantage on case-control status (n = 781).

	Unadj. OR[a],b	95% CI	p	Adj. OR[†]	95% CI	p	Adj. OR[††]	95% CI	p	% of total effect
					Outcome: Case-Control Status					
Parental separation (vs. none)										
Direct effect	2.42	1.71-3.42	<0.001	1.79	1.22-2.61	0.003	1.61	1.09-2.40	0.018	24.6
Total indirect effect	2.46	1.60-3.80	<0.001	4.05	2.06-7.97	<0.001	4.35	2.11-8.95	<0.001	75.4
Specific indirect effects										
No qualifications	1.34	0.99-1.81	0.055	2.21	1.30-3.76	0.003	2.38	1.34-4.20	0.003	44.4
Current disadvantage	1.40	1.18-1.65	<0.001	1.18	1.01-1.39	0.040	1.16	0.99-1.37	0.069	7.7
No qualifications – Current disadvantage	1.32	1.09-1.59	0.004	1.54	1.19-2.00	0.001	1.57	1.20-2.06	0.001	23.3
Total effect	5.95	3.47-10.21	<0.001	7.23	3.45-15.17	<0.001	7.02	3.21-15.35	<0.001	-
Parental death (vs. none)										
Direct effect	2.65	1.31-5.36	0.007	2.71	1.29-5.67	0.008	2.61	1.20-5.67	0.015	71.5
Total indirect effect	1.40	0.69-2.87	0.355	1.37	0.49-3.78	0.546	1.47	0.51-4.24	0.482	28.5
Total effect	3.71	1.37-10.08	0.010	3.70	1.06-12.95	0.040	3.83	1.03-14.20	0.045	-

[†] Adjusted for age, gender, ethnicity, and study centre

[††] Adjusted for age, gender, ethnicity, study centre, and parental history of psychosis

[a] Separation by ethnicity (white British, black Caribbean, and black African) (likelihood ratio test, $\chi^2 = 4.99$, P = 0.661)

White British
Direct effect   Unadj. OR 2.98** (1.59-4.45)
Total indirect effect   Unadj. OR 1.86* (1.10-3.14)
Total effect   Unadj. OR 5.53** (2.83-10.84)
Black Caribbean
Direct effect   Unadj. OR 2.16* (1.07-4.36)
Total indirect effect   Unadj. OR 2.79* (1.06-7.35)
Total effect   Unadj. OR 6.03** (1.87-19.43)
Black African
Direct effect   Unadj. OR 2.14 (0.47-9.81)
Total indirect effect   Unadj. OR 0.92 (0.03-27.44)
Total effect   Unadj. OR 1.97 (0.05-81.04)
* p<0.05, ** p<0.01