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ORIGINAL ARTICLE

Modelling the interplay between childhood and adult adversity in pathways to psychosis: initial evidence from the AESOP study

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Background. There is evidence that a range of socio-environmental exposures is 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 AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) 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 AESOP 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 sociodevelopmental pathway to psychosis.

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Key words: Interaction, mediation, psychosis, social adversity.

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 is 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 make an 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. van Os *et al.* 2004;

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Zammit *et al.* 2010*b*; Bebbington *et al.* 2011). 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 sensitization 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 this, we hypothesize that the high prevalence of linked social adversities over time in certain minority groups accounts for the high rates of psychosis (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 & 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. van Os *et al.* 2004; Clarke *et al.* 2011). 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 & 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 Fig. 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 sociodevelopmental models of psychosis become empirically testable hypotheses.

In light of the above, we sought to extend previous analyses of data from the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) 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 hypothesized 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 was 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: aged 16–64 years; 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

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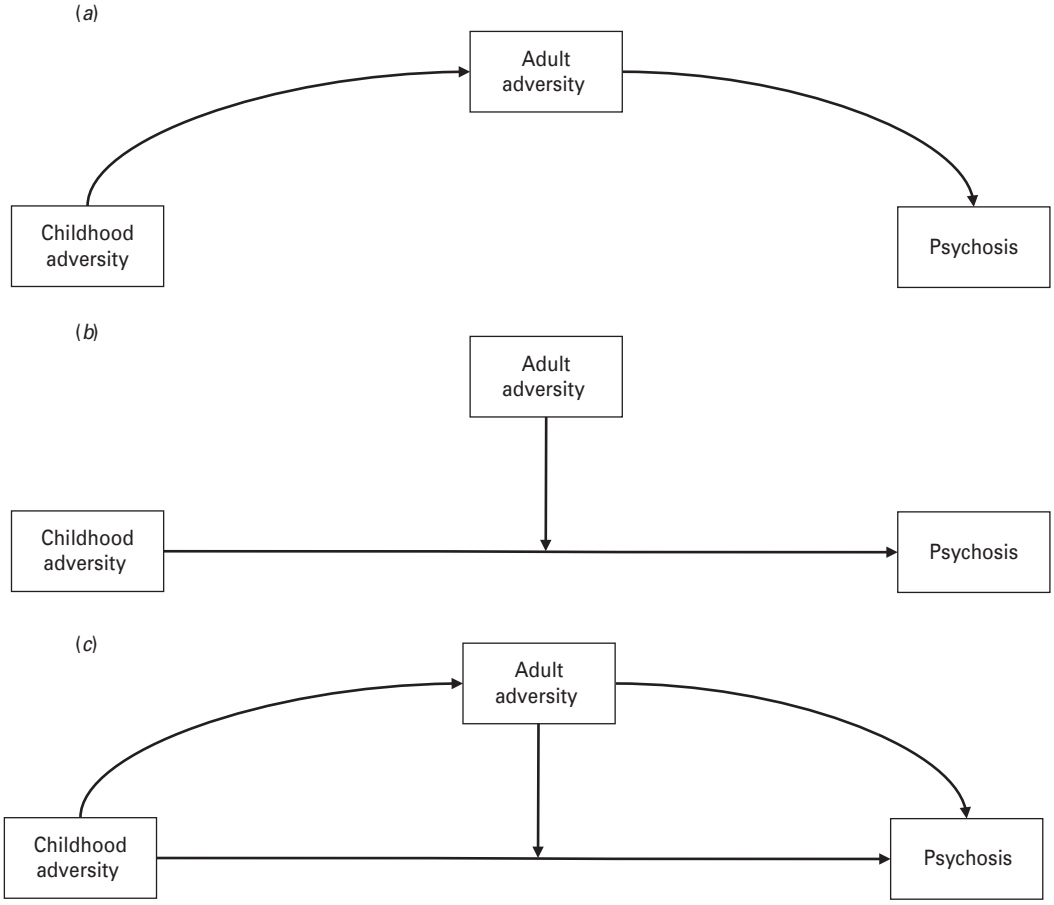

Fig. 1. Models of mediation, synergy and mediated synergy. (*a*) Mediation model. The effect of the primary exposure (childhood adversity) is via its impact on likelihood of exposure to a more proximal exposure (adult adversity). (*b*) Synergy (interaction, effect modification) model. The effect of the primary exposure (childhood adversity) combines with (or depends on) another exposure (adult adversity) to increase risk. (*c*) Mediated synergy model. The primary exposure (childhood adversity) may both (i) (partly) make an impact on psychosis via a more proximal exposure (adult adversity) and (ii) interact with that exposure (adult adversity) to increase risk of psychosis.

as defined by the International Classification of Diseases, 10th revision (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 years 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 (Mallett *et al.* 2002). 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 years (with separation defined as not living in the same household as one or both parents for 1 year or more because of family breakdown); and (2) death of a parent before the age of 16 years (Morgan *et al.* 2007). With regard to current and long-term (i.e. 1 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 dichotomizing 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 operationalized as not having achieved any formal educational qualifications.

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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 (Mallett *et al.* 2002). Symptom data were collected using the Schedules for Clinical Assessment in Neuropsychiatry (World Health Organization, 1992). ICD-10 diagnoses were determined by consensus (Kirkbride *et al.* 2006). Pre-morbid intelligence quotient (IQ) was estimated using the National Adult Reading Test and a parental history of psychosis was established using the Family Interview for Genetic Studies (National Institute of Mental Health, 1992).

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 years 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 (ORs) for total and specific indirect effects of parental separation and parental death through the hypothesized mediators on case-control status were estimated using maximum likelihood (ML) estimation in MPlus, version 6.1 (Muthén & Muthén, 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 the use of bias-corrected bootstrapping (MacKinnon, 2008; Preacher & Hayes, 2008). Findings from these analyses (see online Supplementary material) were in line with those produced using logit coefficients and ORs, 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 (ICRs), as described by Schwartz (2006). Under the assumption that when the disorder is rare ORs approximate risk ratios, this approach uses ORs to estimate the relative excess risk due to interaction, i.e.

$$\mathrm{ICR} = \mathrm{OR}_{\text{exposure A \& exposure B}} - \mathrm{OR}_{\text{exposure A only}} - \mathrm{OR}_{\text{exposure B only}} + 1.$$

In this model, deviation from additivity (i.e. interaction) is indexed by an ICR greater than 0. Confidence intervals (CIs) and p values for ICRs were generated using the NLCOM procedure in Stata (StataCorp LP, USA).

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 AESOP study over a 3-year period. Basic sociodemographic 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 [adjusted OR (aOR) 2.45] and death of a parent (aOR 3.06) and (*b*) all current and long-term indicators of social disadvantage (aORs ranged from 2.11 to 7.50) (Morgan *et al.* 2007, 2008). 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 three times more likely to have no formal qualifications (aOR 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.

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Table 1. *Basic sociodemographic and diagnostic characteristics by case-control status*

	Controls (n=391)	Cases (n=390)	t	χ^2	df	p
Mean age, years (S.D.)	37.3 (12.5)	30.5 (10.8)	8.20		779	<0.001
Mean self-esteem[a] (S.D.)	39.2 (7.6)	36.2 (7.8)	4.48		533	<0.001
Gender, *n* (%)						
Male	161 (41.2)	218 (55.9)		16.94	1	<0.001
Female	230 (58.8)	172 (44.1)				
Ethnicity, *n* (%)						
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, *n* (%)						
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, *n* (%)						
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, *n* (%)						
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, *n* (%)						
No	384 (98.2)	312 (85.5)		41.9	1	<0.001
Yes	7 (1.79)	53 (14.5)				
Diagnosis, *n* (%)						
Non-affective psychosis	–	263 (67.4)		–	–	–
Affective psychosis	–	127 (32.6)		–	–	–

df, Degrees of freedom; S.D., standard deviation.
[a] Sample size: n=535 (240 cases, 295 controls).

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: aOR 1.61, 95% CI 1.09–2.40; total indirect effect: aOR 4.35, 95% CI 2.11–8.95) (Table 2 and Fig. 2; see Supplementary Table S1 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 scrutinized there was evidence for pathways from separation to psychosis via no qualifications alone (aOR 2.38, 95% CI 1.34–4.20), via adult disadvantage alone (aOR 1.16, 95% CI 0.99–1.37), and via no qualifications and adult disadvantage (aOR 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 CIs were wide, which suggests this may reflect loss of power

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Table 2. *Total, direct, total indirect and specific indirect effects (ORs) of parental separation, educational level and current social disadvantage on case-control status (n=781)*

	Outcome: case-control status									
	Unadjusted OR[a]	(95% CI)	*p*	Adjusted OR[b]	(95% CI)	*p*	Adjusted OR[c]	(95% CI)	*p*	Percentage of total effect
Parental separation (*v.* 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 (*v.* 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	–

OR, Odds ratio; CI, confidence interval.

[a] See Table 3 for estimates stratified by ethnicity.

[b] Adjusted for age, gender, ethnicity and study centre.

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

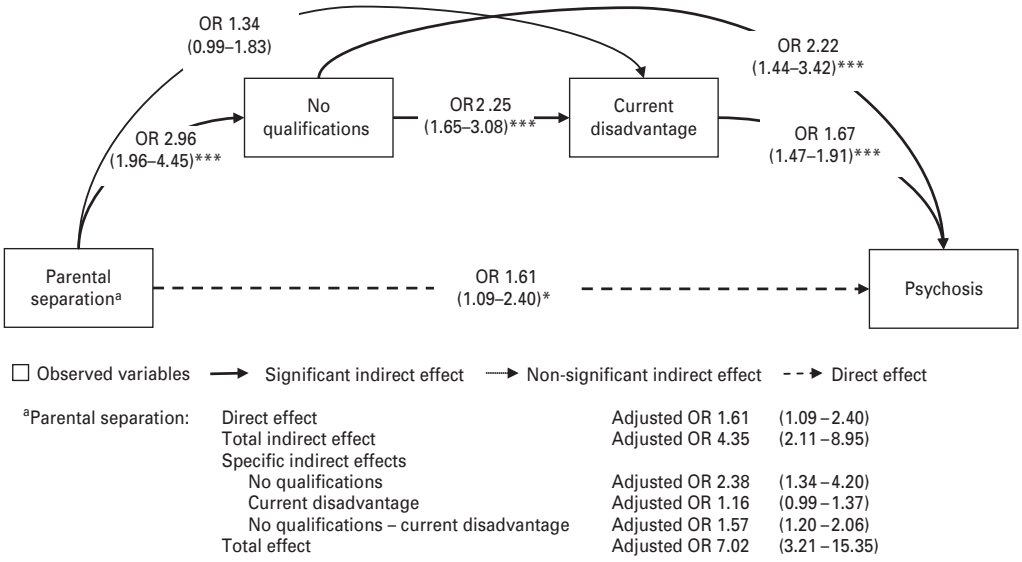

Fig. 2. Path diagram of odds ratios (ORs) and 95% confidence intervals of parental separation, educational level and current social disadvantage on case-control status adjusted for age, gender, ethnicity, study centre and parental history of psychosis (n=781, 65 free parameters). Compared with controls, 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. * p<0.05, *** p<0.001.

(see Table 3). Further, when we repeated the above analyses using (*a*) our index of long-term disadvantage (online Supplementary Tables S2a, S2b) and (*b*) a sample of cases restricted to those with a very-short duration of untreated psychosis (DUP) (1 month or less) (online Supplementary Tables S3a, S3b), 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 subsample 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 subsample the patterns of association and mediation described above broadly held. Second, there was weak evidence (unadjusted 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 (Fig. 3 and Supplementary Tables S4a, S4b).

Mediation (3): accounting for pre-morbid IQ

To assess whether our findings in relation to mediation via education and disadvantage could be accounted for by pre-morbid cognitive deficits, we repeated the relevant analyses above in a restricted sample with data on estimated pre-morbid IQ (n=457) (Supplementary Tables S5a, S5b). 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 pre-morbid 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

Table 3. *Separation of ORs by ethnicity (white British, black Caribbean and black African)*[a]

Ethnicity	Effect	Unadjusted OR (95% CI)
White British	Direct	2.98 (1.59–4.45)**
	Total indirect	1.86 (1.10–3.14)*
	Total	5.53 (2.83–10.84)**
Black Caribbean	Direct	2.16 (1.07–4.36)*
	Total indirect	2.79 (1.06–7.35)*
	Total	6.03 (1.87–19.43)**
Black African	Direct	2.14 (0.47–9.81)
	Total indirect	0.92 (0.03–27.44)
	Total	1.97 (0.05–81.04)

OR, Odds ratio; CI, confidence interval.
[a] Likelihood ratio test: χ^2=4.99, p=0.661.
*p<0.05, ** p<0.01.

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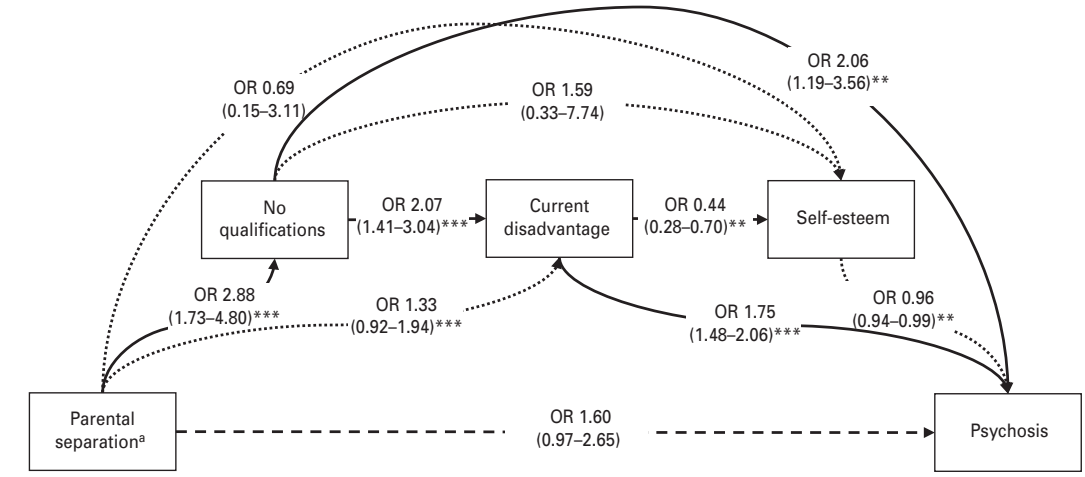

[a]Parental separation:

Direct effect	Adjusted OR 1.60	(0.97 – 2.65)
Total indirect effect	Adjusted OR 3.99	(1.65 – 9.65)
Specific indirect effects		
No qualifications	Adjusted OR 2.15	(1.08 – 4.26)
Current disadvantage	Adjusted OR 1.17	(0.95 – 1.45)
Self-esteem	Adjusted OR 1.01	(0.96 – 1.08)
No qualifications – current disadvantage	Adjusted OR 1.54	(1.10 – 2.14)
No qualifications – self-esteem	Adjusted OR 0.98	(0.92 – 1.05)
Current disadvantage – self-esteem	Adjusted OR 1.01	(0.99 – 1.02)
No qualifications – current disadvantage – self-esteem	Adjusted OR 1.02	(1.00 – 1.05)
Total effect	Adjusted OR 6.41	(2.44 – 16.86)

Fig. 3. Path diagram of odds ratios (ORs) and 95% confidence intervals 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). 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. ** p<0.01, *** p<0.001.

(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 pre-morbid IQ (Supplementary Table S4).

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 dichotomized 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 aOR 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 (95% CI 3.04–10.98) (ICR 3.05, 95% CI –0.62 to 6.72, p=0.103; see Fig. 4 *a*). Turning to separation and disadvantage, there was strong evidence of departure from additivity. The aOR 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 Fig. 4 *b*). 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 pre-morbid IQ and further adjusted analyses for pre-morbid IQ, the interaction between separation and disadvantage was attenuated

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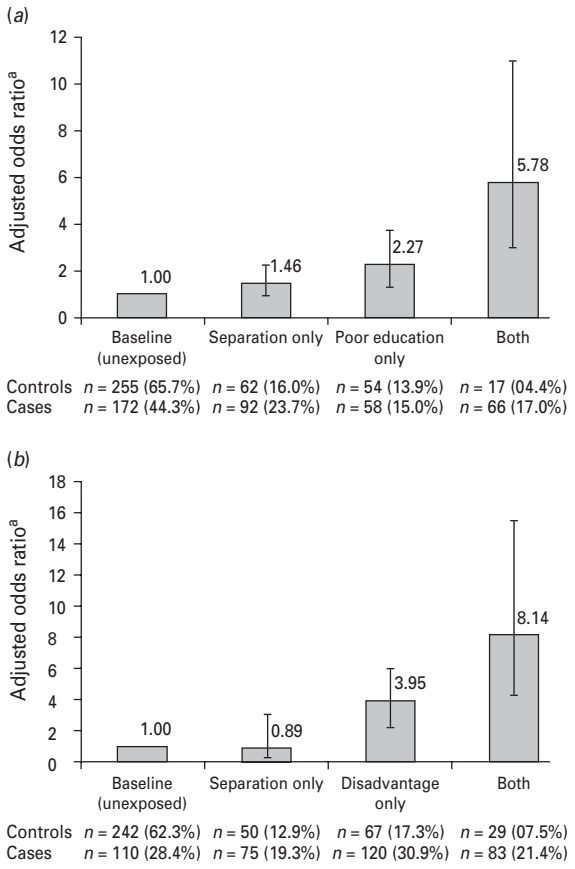

Fig. 4. Additive interactions between separation from a parent and poor education and adult disadvantage. Values are adjusted odds ratios, with 95% confidence intervals (CIs) represented by vertical bars. (*a*) Separation and education. Interaction contrast ratio: 3.05 (95% CI –0.62 to 6.72) (p=0.103). (*b*) Separation and disadvantage. Interaction contrast ratio: 4.30 (95% CI 0.66–7.94) (p=0.021). [a] Odds ratios adjusted for age, gender, ethnicity, study centre and parental history of psychosis.

(ICR 2.83, 95% CI –0.79 to 6.45, p=0.126). This may, however, largely reflect a loss of power, as the estimated ICR remain notably above zero and CIs 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 the loss of a parent during childhood. This, of course, may be due to a lack of power given that 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 the age of 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 the 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 that 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 subsample, for estimated premorbid IQ, and the findings remained largely robust.

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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.* 2010*a*). Recent critiques of interaction analyses, particularly of additive models, emphasize the need to determine analyses and scale for interaction *a priori*, especially given the high probability of type I error (Zammit *et al.* 2010*a*). 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 & 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 that separation indicates exposure to processes that make an impact on the risk of psychosis both directly (e.g. disrupted attachments, intrafamilial 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 an 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 UK Avon Longitudinal Study of Parents and Children birth cohort (n in analyses=6692), found that the effects of harsh parenting and bullying prior to the age of 8.5 years on risk of psychotic experiences at the age of 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 & Kapur, 2009), the hypothalamic–pituitary–adrenal 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.

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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 sociodevelopmental 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).

Unravelling 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 & Morgan, 2012). It may be, then, that by identifying how social (and other) factors that may be amenable 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

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713000767.

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Declaration of Interest

R.M.M. is an editor of *Psychological Medicine*.

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