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Childhood Epstein-Barr Virus infection and subsequent risk of psychotic experiences in adolescence: A population-based prospective serological study

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Abstract

Background—Several studies suggest a link between early-life infection and adult schizophrenia. Cross-sectional studies have reported: (1) increased prevalence of Epstein-Barr Virus (EBV), a member of the Herpesviridae family in schizophrenia; (2) a possible role of Herpes simplex virus in cognitive dysfunction in schizophrenia and healthy controls. We report a longitudinal serological study of early-life EBV infection, childhood IQ, and subsequent risk of psychotic experiences (PE) in adolescence.

Methods—Serum antibodies to EBV (anti-VCA IgG) were measured in 530 participants from the ALSPAC cohort at age 4 years. Assessments for IQ at age 9 and PE at age 13 were attended by 401 and 366 of these individuals, respectively. Logistic regression calculated odds ratio (OR) for PE in EBV-exposed, compared with unexposed group. Mean IQ scores were compared between these groups; effect of IQ on the EBV–PE association was examined. Potential confounders included age, gender, ethnicity, social class, household crowding, and concurrent depression and anxiety.

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Contributors

GMK designed the study, analysed data and wrote the first draft. JS contributed to data analysis and revision of the draft. SZ contributed to data collection, analysis, and revision of the draft. GL and PBJ contributed to study design, analysis, revision, and provided overall supervision for the study.

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Conflict of interest

None of the authors has any conflicts of interest to declare.

Results—About 25% of the sample was exposed to EBV at age 4. EBV exposure was associated with subsequent risk of definite PE in adolescence; OR 5.37 (95% CI 1.71–16.87), which remained significant after confounding adjustment. EBV-exposed individuals compared with unexposed performed worse on all IQ measures; mean difference in full-scale IQ 4.15 (95% CI 0.44–7.87); however, this was explained by socio-demographic differences. The EBV–PE association was not explained by IQ.

Conclusions—Early-life exposure to EBV is associated with PE in adolescence, consistent with a role of infection/immune dysfunction in the aetiology of psychosis.

Keywords

Epstein-Barr Virus; Herpes Simplex Virus; IgG antibody; Serology; IQ; Neurodevelopment; Psychotic experiences; Schizophrenia risk; ALSPAC birth cohort

1. Introduction

A role for viral infection in the pathogenesis of schizophrenia was proposed nearly a century ago (Menninger, 1926). Recent longitudinal studies have linked serologically determined prenatal maternal infection with Herpes Simplex Virus type 2 (HSV-2) (Buka et al., 2001a; Buka et al., 2008; Mortensen et al., 2010), influenza (Brown et al., 2004a), or cytomegalovirus (CMV) (Blomstrom et al., 2012) with the risk of schizophrenia in adult offspring in some but not all cohorts (Brown et al., 2006; Mortensen et al., 2007); for a systematic review see Khandaker et al. (2013). Viral infection of the CNS during childhood has also been associated with the risk of adult psychotic illness (Rantakallio et al., 1997; Dalman et al., 2008; Khandaker et al., 2012). Epstein-Barr Virus (EBV) is a member of the Herpesviridae family, and is potentially neurotropic (Schmutzhard, 2001). However, studies of EBV and psychiatric risk are limited. Two cross-sectional studies have reported increased sero-prevalence of EBV in psychiatric disorders (Gotlieb-Stematsky et al., 1981) including schizophrenia (Delisi et al., 1986). Recently, an association between EBV sero-positivity and self-reported psychotic experiences (PE) in adolescents has also been reported (Wang et al., 2011). However, longitudinal studies of EBV and subsequent risk of psychotic outcomes are lacking.

Early-life PE may be important antecedents of adult schizophrenia. Population-based birth cohort studies have reported a substantially increased risk of adult psychotic illness among individuals reporting PE during childhood/adolescence (Poulton et al., 2000; Zammit et al., 2013). Early-life PE are also associated with a number of risk factors for schizophrenia (Horwood et al., 2008; Thomas et al., 2009; Zammit et al., 2009). Thus, it has been suggested that studying these experiences may help to elucidate the pathophysiology of adult psychotic disorders (Kelleher and Cannon, 2011; Murray and Jones, 2012). The neurodevelopmental hypothesis of schizophrenia posits abnormal brain development as a cause of this illness (Murray and Lewis, 1987; Weinberger, 1987). Identification of a linear relationship between IQ deficit in the premorbid period and future risk of schizophrenia is a key piece of evidence underpinning a developmental aspect to the disorder (Jones et al., 1994; David et al., 1997; Khandaker et al., 2011). IQ deficit is present in different stages of schizophrenia and is one of the most important predictors of functional outcome (Gold et al.,

2002). Longitudinal studies have also found cognitive deficits in children who report PE subsequently in childhood/adolescence (Horwood et al., 2008; Polanczyk et al., 2010; Niarchou et al., 2013).

Early-life infection is a plausible candidate for neurodevelopmental insult. Therefore, it is possible that infection leads to IQ deficit, which in turn increases subsequent risk of psychotic outcomes. Such an explanatory model would view IQ deficit as a risk mediator. This is consistent with the evidence linking exposure to HSV-1 with cognitive dysfunction both in schizophrenia (Dickerson et al., 2003) and healthy individuals (Watson et al., 2012). Alternatively, IQ deficit may arise from the interplay between infection and psychosis risk. This is in line with a previous study reporting lower childhood verbal IQ in prenatal maternal influenza-exposed cases of adult schizophrenia, compared with the unexposed cases (Ellman et al., 2009). Therefore, studies of early-life infection, subsequent IQ, and PE may help to elucidate the underlying pathways to schizophrenia or cognitive dysfunctions that are integral parts of the disorder. To our knowledge, no general population longitudinal study has examined whether childhood neurocognitive deficit associated with early-life infection mediates the risk of subsequent PE.

Using data from the general population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report associations between serologically confirmed exposure to EBV at age 4 years, IQ at age 9 years, and risk of PE at age 13 years. We predicted that EBV exposure would be associated with subsequent PE, and IQ deficit would explain this association.

2. Methods and materials

2.1. Sample selection

The ALSPAC birth cohort comprises 14,062 live births from pregnant women resident in the county of Avon, a geographically defined region in the southwest of England, with expected dates of delivery between April 1991 and December 1992 (www.bristol.ac.uk/alspac/). Parents have completed regular postal questionnaires about all aspects of their child's health and development from birth. Since age 7, the children have attended an annual assessment clinic during which they participate in a range of face-to-face interviews and physical tests.

When the cohort was four years of age, gastroenterologists interested in the transmission of *Helicobacter pylori* invited a randomly selected subsample (approximately 10%) for a serological study. Those who attended were broadly representative of the entire cohort in terms of socio-demographic characteristics including gender, ethnicity, and social class. In total, 530 children completed serological assays, which formed the risk set for the current study. The assessments for IQ at age 9 years and PE at age 13 years were attended by 401 and 366 of these individuals, respectively. The EBV–IQ and EBV–PE associations were examined using these maximum available samples. Complete data on EBV, IQ, and PE were available for 336 individuals, which formed the sample for mediation analyses.

2.2. Ethical approval

Ethical approval for the study was obtained from ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

2.3. Assessment of psychotic experiences

PE were identified through the face-to-face, semi-structured Psychosis-Like Symptom Interview (PLIKSi) conducted by trained interviewers in assessment clinics at age 13 years. In total 6455 individuals were assessed (Horwood et al., 2008), of which 366 had provided serological data on EBV at age 4 years. The PLIKSi drew on the Diagnostic Interview Schedule for Children—IV (DISC-IV) (Shaffer et al., 2000), and the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN 2.0) (WHO, 1994). It has good inter-rater reliability ($\kappa = 0.7$) (Horwood et al., 2008). Twelve symptoms covering the three main domains of ‘positive’ psychotic experiences were elicited: hallucinations (visual and auditory); delusions (spied on, persecution, thoughts read, reference, control, grandiosity, and others); and experiences of thought interference (insertion, withdrawal, and broadcasting).

The interviewer recorded presence of any PE occurring in the last six months (coded as not present, suspected, or definitely psychotic), their frequency, and any attributions, such as fever, hypnagogic or hypnopompic state, alcohol or drugs. This allowed an observer-based rating for three binary outcomes, with decreasing prevalence: (a) ‘any PE (suspected or definite)’; (b) ‘definite PE’; and (c) ‘definite PE without attributions’. The risk of each outcome was analysed separately. The comparison group for each outcome included all individuals who did not meet the definition for that outcome. For example, individuals with suspected PE were included in the comparison group for the outcome of definite PE, along with those with no PE.

The interviews were carried out by 13 psychology graduates trained in the SCAN (psychosis section) and PLIKSi. They were trained by two experienced clinicians and SCAN trainers (a child psychiatrist and a general adult psychiatrist). Interviewers used cross-questioning to establish the presence of symptoms coded according to the glossary definitions and rating rules for SCAN. Uncertain responses after probing were always “rated down”, and symptoms were rated as definite only when a clear example was provided. At regular intervals, a psychiatrist rated samples of recorded interviews to ensure that the PE were rated correctly (Horwood et al., 2008).

2.4. Assessment of EBV exposure

Blood samples were collected at age 4 years following standard procedure. Since the original serological study was focused on the route of transmission for *H. pylori*, antibodies to EBV and hepatitis A virus were also measured as these reflect oral–oral and faecal–oral exposure, respectively. Antibodies for no other infectious agents were tested. Due to our hypothesis driven approach, we have only analysed the data for EBV (N = 530).

Immunoglobulin G antibodies to viral capsid antigen (anti-VCA IgG) to EBV was measured by indirect immunofluorescence test. Individuals were classed as seropositive or negative.

The presence of anti-VCA IgG reflects exposure to EBV anytime in the past. Details of the assay, such as antibody concentration in individual participants, specificity of test are lost.

2.5. Assessment of IQ

IQ was measured by the Wechsler Intelligence Scale for Children (WISC III, 3rd UK edition) at average age 9 years (Wechsler et al., 1992). A shortened version of the test was applied by trained psychologists, whereby only alternate items were used for all subtests, with the exception of the coding subtest which was administered in its standard form.

2.6. Assessment of covariates

Gender, ethnicity, paternal social class, measures of household crowding, and age, depression and anxiety at the time of assessment of PE were included as potential confounders. As per the UK Office of National Statistics (ONS) classification system paternal social class was recorded in six categories, in descending order: Social class I = professionals and higher managerial workers; II = intermediate occupations; III = skilled occupations, divided into two groups as non-manual and manual; IV = partly skilled occupations; V = unskilled occupations (Classification of occupations and coding index, 1980). The total number of adults and children living in the house (separately, both grouped as 0, 1, 2, and 3) and total number of living rooms in the house excluding kitchen were used as markers of household crowding. Total score from the short version of the Mood and Feelings Questionnaire (MFQ) was used as a measure of depression and anxiety at age 13 years. The MFQ is a validated tool widely used in epidemiological studies (Angold et al., 1995). It includes 13 items covering core symptoms of depression and anxiety experienced in the past two weeks, each coded as zero (not true), one (sometimes true) or two (true) giving a total score of 0–26.

2.7. Statistical analysis

Logistic regression was used to calculate odds ratios (OR) for PE at age 13 years in the EBV-exposed, compared with unexposed group at age 4 years. Regression models were adjusted for age and total MFQ score at the time of assessment of PE, gender, ethnicity, paternal social class, and measures of household crowding.

Linear regression was used to compare mean difference in IQ score (full-scale, verbal and performance) at age 9 years between those exposed and unexposed to EBV at age 4 years. Regression models were adjusted for age at IQ assessment, gender, paternal social class and ethnicity.

We examined the relationships between EBV infection, IQ, and the strictest outcome, i.e. definite PE without attributions in two ways: (1) whether the EBV–PE association could be explained by IQ deficit (i.e. mediation); (2) whether IQ deficit was present in individuals with PE only if they were exposed to EBV (i.e. interaction between EBV and PE). For mediation, first, separate regression models assessed the association between: (1) exposure (EBV) and outcome (PE); (2) exposure and mediator (total IQ score); (3) mediator and outcome controlling for exposure. Finally, the exposure–outcome, exposure–mediator, mediator–outcome regression lines were fitted simultaneously in a single model. We

expected, in the final step, that the EBV–PE relationship would be attenuated (partial mediation), or eliminated (complete mediation) (Baron and Kenny, 1986). In case of partial mediation, the extent to which EBV–PE estimate was attenuated after inclusion of IQ was calculated. For interaction, an interaction term (EBV * PE) was included in the linear regression model of IQ (dependent variable) as well as EBV and PE as separate independent variables.

3. Results

Out of 530 children assessed, 134 (25.3%) were seropositive to EBV at age 4 years. There was no significant difference in socio-demographic characteristics between those exposed and unexposed to EBV (Table 1).

3.1. Risk of psychotic experiences at age 13 years

Out of 366 individuals with data on both EBV and PE, 24.3% were exposed to EBV. The proportion of all types of PE at age 13 years was higher in the EBV-exposed, compared with the unexposed group age 4 years (Table 2).

Exposure to EBV at age 4 years was associated with over five-fold risk of definite PE at age 13 years (Table 3). The odds ratios remained statistically significant after adjustment for potential confounders. In the fully adjusted model the odds ratios nearly doubled in size, most likely due to small number of individuals with PE (see Discussion section).

3.2. Association with IQ at age 9 years

Out of 401 children with data for both EBV and IQ, 23.4% were exposed to EBV. Children exposed to EBV performed worse on all measures of IQ compared with the unexposed. However, there was only weak evidence that mean IQ scores differed between two groups after adjustment for confounders (Table 4).

3.3. Relationship between childhood IQ, early-life EBV exposure, and PE in adolescence

In the sample of 336 with complete data on EBV, total IQ, and PE: (1) exposure to EBV was associated with PE (dependent variable) ($\beta = 1.63$, $SE = 0.66$, $p = 0.01$). (2) Association between EBV and total IQ (dependent variable) fell short of conventional statistical significance ($p = 0.08$). (3) Total IQ was associated with PE (dependent variable) after controlling for EBV ($p = 0.04$). Finally, after inclusion of IQ as a potential mediator in the logistic regression model, the EBV–PE association was slightly attenuated but still remained significant ($\beta = 1.55$, $SE = 0.66$, $p = 0.02$). This equated to only about 5% attenuation of the effect estimate, suggesting that the association between EBV and PE was not mediated by IQ deficit.

The interaction term in the linear regression model of IQ was not significant ($p = 0.45$), indicating no evidence for an interaction between early-life EBV infection and risk of adolescent PE in determining childhood IQ.

4. Discussion

Findings from this population-based longitudinal study suggest that serologically confirmed EBV infection in early childhood, as measured by the presence of anti-VCA IgG in serum is associated with definite PE in adolescence. This is independent of a number of potential socio-demographic confounders as well as household crowding, concurrent depression and anxiety. To our knowledge, this is the first longitudinal study linking exposure to EBV with subsequent risk of psychotic outcomes. Thus, the findings need replication.

The findings are consistent with previous studies reporting an association between early-life infection and adult psychotic illness (Brown and Derkits, 2010; Khandaker et al., 2013). Since the human brain continues to develop throughout childhood and well into early adulthood (de Graaf-Peters and Hadders-Algra, 2006), infection during this period especially with neurotropic agents could potentially increase the risk of a range of neurodevelopmental outcomes. A recent meta-analysis suggests nearly two-fold increased risk of adult psychotic disorder for childhood CNS viral infection (Khandaker et al., 2012). It is important to note that the outcome of this study was PE in adolescence rather than diagnosis of schizophrenia. However, several lines of evidence suggest that early-life PE may provide a valid paradigm for studying the development of adult psychotic illness (Kelleher and Cannon, 2011; Murray and Jones, 2012). Longitudinal studies have reported up-to 16-fold risk of adult psychotic disorder among individuals reporting PE in childhood (Poulton et al., 2000; Zammit et al., 2013). PE are associated with a number of risk factors for schizophrenia, such as prenatal maternal infection and obstetric complications (Zammit et al., 2009), poorer childhood IQ (Horwood et al., 2008), and other markers of aberrant neurodevelopment (Khandaker et al., in press), and childhood atopic disorders (Khandaker et al., 2014). PE in the general population and that observed in psychotic disorders may exist in a continuum (van Os et al., 2009). Finally, neurophysiological studies suggest common underlying mechanisms for PE seen in healthy people and in schizophrenia (Howes et al., 2013).

Previous studies have reported an association between Herpes Simplex Virus (HSV-1) and cognitive dysfunction in schizophrenia (Dickerson et al., 2003; Yolken et al., 2011), and in healthy individuals (Watson et al., 2012). Decline in executive function and grey matter loss over time among HSV-1-exposed first-episode schizophrenia patients has also been reported (Prasad et al., 2011). Another serological study have reported lower childhood verbal IQ in prenatal maternal influenza-exposed, compared with the unexposed cases of adult schizophrenia (Ellman et al., 2009). However, the EBV–PE association could not be attributed to deficit in childhood IQ in our sample. There was also no evidence that interplay between EBV and PE led to changes in IQ. An explanation for this could be the study outcome, i.e. PE rather than diagnosis of schizophrenia. Adolescent participants with PE are almost certainly a heterogeneous group. In many cases these symptoms are likely to be part of development, whilst in some they might indicate brain pathology (De Loore et al., 2011; Rubio et al., 2012). Thus, any underlying biological effect (such as mediation by IQ) may have become diluted. It is also possible that CNS alterations from early-life infection that lead to increased risk of psychotic outcomes is independent of cognitive performance, as measured by IQ tests. Other mechanisms may involve inflammatory and genetic pathways.

The longitudinal design is a strength of this study. Serological assessment for exposure to EBV was carried out several years before the outcome of PE, thus, eliminating the possibility of reverse causality. Details of assay method, such as specificity of test, or data on antibody concentration in individual participants are now lost. This is an important limitation, and the results need to be interpreted with caution. We no longer have the serum samples from age 4 years to repeat EBV assays. Future studies should include adequate descriptions of laboratory assays. Lack of specific details also precludes any comment on whether the infection might have been active at time of exposure measurement. Nevertheless, the presence of anti-VCA IgG in serum at age 4 years indicates exposure to EBV anytime in the past. Thus, the findings are consistent with a longitudinal association between early-life exposure to EBV and subsequent risk of psychotic outcomes. Environmental factors associated with exposure are similar for several members of the Herpesviridae family, such as family size and social class. Although some of these factors were controlled for in regression modelling, antibodies to no other relevant infections, such as HSV-1, 2, or CMV were assayed, which would have made the conclusions regarding EBV much stronger.

Low statistical power arising from small sample size and relative rarity of PE is an issue. This is reflected in wide confidence intervals around the ORs (Table 3). In logistic regression ORs can become inflated after adjusting for multiple confounders especially when there are small numbers in some cells. This is likely to be the case for the fully adjusted ORs; for example, the fully adjusted model included only eight cases of definite PE without attributions (Table 3). Therefore, we emphasise on the unadjusted ORs. However, it is worth noting that the ORs remained statistically significant after confounding adjustment.

Limitations of the study also include missing data. Out of 530 individuals who were assayed for EBV at age 4 years, 164 did not attend the assessment for PE at age 13 years. EBV exposure was similar between those with or without data on psychotic outcomes (about 25% in both groups). If the outcome were better in EBV-exposed individuals with missing data for PE (i.e. fewer developed PE), there would be a possibility of spurious over-estimation of the EBV–PE association. However, there was no reason to believe that this was the case. There was an over-representation of individuals from lower social classes in the missing sample. In ALSPAC, lower social class was associated with higher risk of PE, lower IQ, and overall, poorer health outcomes.

Potential mechanisms for psychotogenesis from exposure to EBV may include effects of inflammatory cytokines on the brain following activation of the innate immune system. Circumstantial evidence for this notion comes from studies of schizophrenia. Increased inflammatory markers in maternal circulation during pregnancy have been previously linked with risk of psychosis in adult offspring (Buka et al., 2001b; Brown et al., 2004b). Animal studies also suggest a role of prenatal inflammation in the aetiology of psychotic illness (Meyer and Feldon, 2010). Acute psychosis is associated with increased proinflammatory cytokines in serum, such as IL-6 (Miller et al., 2011), and microglial (CNS immune cells) activation in PET scans of the brain (van Berckel et al., 2008). Thus, it is possible that early-life infection primes microglia for an exaggerated response to subsequent infections with adverse consequences for neuronal survival and functioning (Hickie et al., 2009). It has been

suggested that some genetic vulnerability to psychosis may be explained by genetic vulnerability to infection (Torrey et al., 2006; Stefansson et al., 2009). It is also possible that genes affecting immunity lead to distinct inflammatory response following infection, which in turn contributes to altered brain function and development. In the future, longitudinal epidemiological studies with genetic and immunological data in addition to detailed phenotypic characterisation are required to test his hypothesis.

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Table 1

Baseline characteristics of individuals exposed and unexposed to EBV at age 4 years.

Group characteristics	Exposed to EBV	Unexposed	χ^2 statistic; p-value
Total number (%)	134 (25.3)	396 (74.7)	-
Age at assessment of PE–mean (SD) in years	12.72 (0.15)	12.73 (0.17)	0.70; 0.48 ^a
Gender–male, n (%)	74 (55.2)	233 (58.80)	0.54; 0.48
Ethnicity–British White, n (%)	127 (98.4)	383 (98.5)	2.67; 0.61
Social class, n (%)			4.65; 0.46
I	7 (6.5)	48 (13.2)	
II	42 (38.9)	139 (38.3)	
III non-manual	10 (9.3)	37 (10.2)	
III manual	36 (33.3)	98 (27.0)	
IV	11 (10.2)	33 (9.1)	
V	2 (1.9)	8 (2.2)	
Number of children in household (%)			4.67; 0.09
0	0	0	
1	15.2	10.7	
2	44.8	56.6	
3	40.0	32.7	
Number of adults in household (%)			1.54; 0.67
0	1.0	0.3	
1	5.8	8.5	
2	88.5	86.3	
3	4.8	4.9	
Number of living rooms excluding kitchen (%)			0.62; 0.75
1	50.0	47.6	
2	35.4	39.2	
3	14.6	13.2	
Total MFQ score at assessment of PE–mean (SD)	4.35 (3.92)	4.37 (3.76)	0.05; 0.96 ^a

Note: Not all 530 individuals had data on all covariates.

^aIndependent sample t-test statistic and p-value.

Table 2

Psychotic experiences (PE) at age 13 years among those exposed and unexposed to EBV at age 4 years.

Outcome Exposure	Any PE, n (%)		Definite PE, n (%)		Definite PE without attributions, n (%)	
	Yes	No	Yes	No	Yes	No
EBV-exposed	15 (16.9)	74 (83.1)	8 (9.0)	81 (91.0)	7 (7.9)	82 (92.1)
EBV-unexposed	30 (10.8)	247 (89.2)	5 (1.8)	272 (98.2)	4 (1.4)	273 (98.6)

Table 3

Exposure to EBV at age 4 years and risk of psychotic experiences (PE) at age 13 years.

Adjustment for confounding	Total sample and number (%) with each outcome				Odds ratio (95% CI) for each outcome		
	Total sample	Any PE	Definite PE	Definite PE without attributions	Any PE	Definite PE	Definite PE without attributions
Unadjusted	366	45 (12.3)	13 (3.5)	11 (3.0)	1.67 (0.85–3.27)	5.37 (1.71–16.87)	5.82 (1.66–20.39)
Age	366	45 (12.3)	13 (3.5)	11 (3.0)	1.66 (0.85–3.26)	5.33 (1.69–16.75)	5.83 (1.66–20.54)
Gender	366	45 (12.3)	13 (3.5)	11 (3.0)	1.65 (0.84–3.24)	5.25 (1.66–16.60)	5.68 (1.60–20.14)
Ethnicity	363	44 (12.1)	13 (3.5)	11 (3.0)	1.77 (0.90–3.48)	5.47 (1.74–17.22)	5.93 (1.69–20.80)
MFQ score	362	44 (12.1)	12 (3.3)	10 (2.7)	1.50 (0.73–3.10)	4.70 (1.37–16.06)	4.94 (1.28–19.02)
Social class	337	42 (12.4)	12 (3.5)	10 (2.9)	1.82 (0.90–3.69)	4.65 (1.42–15.20)	4.91 (1.34–17.99)
Household crowding ^a	331	42 (12.6)	12 (3.6)	10 (3.0)	1.75 (0.86–3.57)	5.72 (1.65–19.87)	6.20 (1.56–24.57)
Fully adjusted ^b	303	38 (12.5)	10 (3.3)	8 (2.6)	1.84 (0.81–4.17)	9.94 (1.67–58.96)	9.54 (1.12–81.51)

^aHousehold crowding includes the number of children and adults living in the house, and the number of living rooms excluding kitchen in the house.

^bThe fully adjusted model includes age at the time of assessment of PE, gender, social class, ethnicity, measures of household crowding, and total MFQscore at age 13 years as potential confounders.

Table 4

IQ at age 9 years in groups exposed and unexposed to EBV at age 4 years.

Measure of IQ	Exposed to EBV		Unexposed		Mean difference (95% CI)	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted ^a
Total IQ	94	102.34 (15.20)	303	106.49 (16.23)	4.15 (0.44, 7.87)	2.42 (−1.40, 6.25)
Verbal IQ	94	106.29 (16.66)	303	109.44 (16.69)	3.14 (−0.72, 7.02)	1.05 (−2.95, 5.05)
Performance IQ	94	97.32 (15.56)	307	101.16 (17.12)	3.83 (−0.04, 7.72)	3.28 (−0.79, 7.35)

^a Adjusted for age at the time of IQ assessment, gender, social class, and ethnicity.