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Variation by Diagnostic Subtype in Risk for Autism Spectrum Disorders Associated with Maternal Parity among Finnish Births

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Abstract

Background—Associations between maternal parity and outcomes in offspring may provide evidence for involvement of prenatal exposures. The objective of this study was to determine whether risk for autism spectrum disorders (ASD) is associated with maternal parity.

Methods—Diagnoses of childhood autism, Asperger syndrome, and pervasive developmental disorder, not otherwise specified (PDD-NOS) were examined separately and as a group. The study was conducted in the Finnish Prenatal Study of Autism, which is based in a national birth cohort. Children born in Finland in 1987–2005 and diagnosed with ASD by 2007 were identified through the Finnish Hospital Discharge Register. Four matched controls were selected for each case using the Finnish Medical Birth Register. The association between parity and each ASD was determined using conditional logistic regression and adjusted for number of children in the sibship and other potential confounders.

Results—ASDs combined showed a pattern of decreasing risk with increasing parity (OR for fourth or greater versus first-born children, 0.43; CI, [0.35, 0.51]). For childhood autism, an adjusted odds ratio (OR) of 1.51 [95% confidence interval (CI), 1.27, 1.81] was observed for second versus first-born children. Associations for Asperger syndrome and PDD-NOS were consistent with those for all ASDs.

Conclusions—Differences in patterns of association between maternal parity and ASD subtypes may indicate varying contributions of specific environmental factors to risk; however, differences in diagnosis or in treatment seeking for childhood behavioural problems cannot be ruled out, particularly for higher-functioning cases.

Autism spectrum disorders (ASD) are developmental disorders involving impaired social interaction and communication, restricted interests, and repetitive behaviours, believed to stem from a combination of genetic and environmental factors.¹ Numerous studies have reported associations of ASDs with maternal parity or child birth order, most often showing greatest risk in children born first^{2–7} and/or 4th or later.^{3, 6, 7} Decreasing risk with increasing parity has also been reported in multivariable adjusted models,^{8–10} though some have found different patterns of association^{11, 12} or no association.¹³ However, interpretation is not clear owing in part to heterogeneity of methods. Notably, studies with sibling control groups tend

to have been small, earlier, and clinic-based; while more recent large, population-based studies have not incorporated sibling information.

Potential explanations for associations of ASDs with parity fall into three categories. First, and of greatest interest with regard to identifying environmental risk factors for ASDs, are mechanisms whereby the experience of one pregnancy changes foetal exposures in the next. Examples of factors observed to be associated with parity include maternal cardiac function,¹⁴ pre-eclampsia,¹⁵ first trimester steroid hormone levels^{16, 17} and maternal health behaviours including smoking¹⁸ and binge drinking.¹⁹ Additionally, maternal body burden of lipophilic chemicals declines with duration of lactation,²⁰ so would tend to be higher in non-parous than parous women. Conversely, caregiving for young children increases exposure to certain infectious diseases,^{21, 22} which could place offspring of parous women at greater risk. Second, the association may be due to confounding by factors generally associated with family size²³ including socio-demographic characteristics or those related to fertility. Third, a health condition (such as an ASD) in one child may alter parents' ensuing reproductive behaviour. This could effectively induce selection bias if the probability of the birth of additional children to a given woman depends on both risk of ASD (children with an affected sibling are at increased risk themselves)²⁴ and maternal parity. If this is the case, the parity-ASD association should vary with size of the family.

Distinguishing between these possible explanations may help identify candidate environmental exposures for autism. We therefore examined the association between maternal parity and risk for ASDs in a large Finnish population, addressing potential confounding and effect modification by number of siblings. The three major subtypes of ASD—childhood autism, Asperger syndrome and pervasive developmental disorder, not otherwise specified (PDD-NOS)—were examined separately and in total.

Methods

Data sources and identification of subjects

ASD cases and controls were identified through the Finnish Prenatal Study of Autism (FIPS-A), a nested case-control study based on a national birth cohort of the 1,149,270 births in Finland from 1987–2005, which has been described previously.²⁵ Data in the FIPS-A were linked between registries using unique personal identity codes. The registries used in this study collect and maintain information about Finnish residents and their use of health services, which are free or of minimal charge. Data used here came from three registries. The Finnish Hospital Discharge Register (FHDR) includes all public and private inpatient diagnoses since January 1, 1967 and outpatient diagnoses since January 1, 1998. The Finnish Medical Birth Register (FMBR) includes comprehensive data on the pre-, peri- and neonatal periods up to age 7 days for all births in Finland. The Finnish Central Population Register (CPR) is a computerized national register containing basic information including name, personal identity code, address, municipality of residence, citizenship, family relations and date of birth and death.

In the FIPS-A, children born in 1987–2005 and diagnosed with ASD by the end of 2007 were identified through the FHDR. Diagnoses in the FHDR are based on the International Classification of Diseases (ICD). ICD-9 was used from 1987–1995 and ICD-10 was used beginning in 1996. The most recently registered diagnosis was used. The diagnostic categories included in this study and their ICD-10 codes were: childhood autism (F84.0), Asperger syndrome (F84.5), and other pervasive developmental disorder and PDD-NOS (F84.8 and F84.9). Diagnoses based on ICD-9 codes (299.0, 299.8 and 299.9) were used to identify 19 cases and their diagnoses were updated to ICD-10 diagnostic classifications. A recent validation study showed that the specificity of childhood autism diagnosis in the

FHDR is high.²⁶ Four controls were selected from the FMBR for each case, matched by date of birth (+/- 30 days), place of birth (first, birth hospital; or second, regional hospital district), sex and residence in Finland. Matching on sex was conducted to ensure a balanced sample given the high male preponderance of ASDs; the other matching criteria were applied to ensure that the controls for each case were representative of the population at risk.²⁴ The exclusion criteria for population controls were ASD or severe/profound mental retardation according to the FHDR. Sibships were identified for subjects based on shared biological mother by linkage to the CPR using the personal identity code of each mother. All offspring linked with the code of each subject mother were identified from the CPR. These data were used to determine the number of children per sibship. For 99.9% of subjects, the sibship size determined using the CPR matched the total number of children recorded for the mother, indicating high reliability.

Exposure and covariates

Data on maternal parity were collected from the FMBR which includes mother's and child's personal identification numbers and information on maternal background, pregnancy, delivery and early neonatal outcomes. Parity was defined as the number of previous live births (categorized as 0, 1, 2, and 3 or more.) Covariates included number of children in the sibship, maternal and paternal ages at birth, maternal smoking during pregnancy, and maternal and paternal psychiatric diagnoses and were selected based on potential association with both maternal parity and ASDs. Data on covariates were obtained from the FMBR, the CPR and the FHDR. Number of children in the sibship was determined using the CPR (categorized as 1, 2, 3 and 4 or more.) Maternal and paternal ages at birth (see Table 1) and maternal smoking during pregnancy were determined using the FMBR. Maternal and paternal psychiatric diagnoses were determined through linkage to the FHDR and treated dichotomously for each parent, based on the ICD-10/9 codes F10-F99 (excluding F70-F79)/291-316 (excluding 293-294). Diagnoses of co-morbid mental retardation (MR) in cases was determined using the FHDR, based on the ICD-10/9 codes F70/317, F71/318.0, F72/318.1, F73/318.2, F78 (no ICD-9 code), and F79/319.

Statistical Methods

To assess the association between parity and ASD, cases were compared with matched population controls. Demographic and parental characteristics listed in Table 1 were tabulated among all observations with non-missing data for each variable and compared by ASD subtype for cases and controls using chi-squared or Fisher's exact tests. Numbers of observations with missing data are noted in the footnote to Table 1. Conditional logistic regression of matched case-control sets was used to determine the association of each ASD with parity. The following models were fit: a) unadjusted; b) adjusting for sibship size; and c) adjusting for sibship size and additional potential confounders, which were included in the adjusted models based on association with ASDs in this cohort (Table 1) and association with parity (χ^2 p-values <0.05 for the association between each categorical covariate and parity; data not shown). These included sibship size, maternal and paternal ages, maternal smoking during pregnancy, and maternal and paternal psychiatric diagnoses. Covariate-adjusted models were also fit after stratifying by co-morbid MR in the cases. To determine whether associations of ASDs with parity varied by family size on a multiplicative scale, models were fit including product terms between sibship size and parity, and significance of product terms as a group were tested in each model using likelihood ratio tests.

To address the possibility that total sibship size may have been misclassified for women who had not yet completed childbearing at the end of the study period, we conducted a supplemental analysis using the covariate-adjusted model ("c", above) restricted to observations where the mother had reached age 45 by the conclusion of the observation

period. All analyses were conducted using SAS statistical software (SAS Version 9.3; SAS Institute Inc., Cary, NC). The study received approval from the Ministry of Social Affairs and Health of Finland and from the Institutional Review Board of the New York State Psychiatric Institute.

Results

Table 1 shows the distribution of characteristics of ASD cases and matched controls by diagnostic sub-category. 79% of the childhood autism, 84% of the Asperger syndrome, and 75% of the PDD-NOS samples were male. Mean (standard deviation) ages in years at diagnosis were 5.5 (3.6) for childhood autism, 9.6 (3.3) for Asperger syndrome and 7.2 (3.4) for PDD-NOS. The median years of diagnosis were 1995, 1993, and 1994 for childhood autism, Asperger syndrome and PDD-NOS, respectively. Oldest parental age categories and presence of psychiatric diagnoses were significantly more frequent among cases for each sub-group. Maternal smoking during pregnancy was more frequent for PDD-NOS cases, less frequent for Asperger syndrome cases, and no different for childhood autism cases relative to subjects from their respective control groups. There was no significant difference in risk of childhood autism by sibship size. Asperger syndrome and PDD-NOS cases were more likely to have no siblings than were their controls (Table 1).

Unadjusted and adjusted associations between maternal parity and each ASD subgroup are shown in Table 2. Combined ASDs showed decreasing risk with increasing parity (p-value for linear trend <0.0001) such that the odds of ASD in a fourth or later-born child (parity=3+) was less than half (OR=0.43) that in a first-born child (parity=0). Patterns for Asperger syndrome (p-value for linear trend <0.0001) and PDD-NOS (p-value for linear trend <0.001) were similar. For *childhood autism*, a significantly elevated OR of 1.51 was observed for second (parity=1) versus first-born children. Analyses stratified by the presence of MR in the cases are presented in Table 3. MR was present in 12.8% of all ASD cases, including 28.9% with childhood autism and 14.1% with PDD-NOS. Because only 1.4% of Asperger syndrome cases were diagnosed with MR these analyses are not shown. Odds ratios for the associations between maternal parity and ASD estimated including only cases without MR were similar to those obtained using the entire sample. There were no significant (p <0.05) associations between maternal parity and ASDs among cases with co-morbid MR. However, ORs for the association of all ASDs (as well as PDD-NOS and childhood autism) co-morbid with MR exceeded 1.0 for second versus first-born children, contrary to the decreased risks of all ASDs and PDD-NOS without co-morbid MR observed for second-born children.

In the test for effect modification, product terms for parity by sibship size were not significant in any model (likelihood ratio test p-values: p=0.88, total ASDs; p=0.31, childhood autism; p=0.08, Asperger syndrome; p=0.67, PDD-NOS), indicating no significant differences in the association between parity and ASD by sibship size. Stratum-specific ORs by sibship size exhibited a similar pattern to those combined across the full population. For all ASDs, Asperger syndrome and PDD-NOS, risk was highest in first-born children across all sibship sizes, and generally decreased with increasing parity. For childhood autism, risk was highest in second-born children from families of two (OR=1.65) or three (OR=1.50) children only.

The patterns of association between ASDs and parity were consistent with those observed among women who had reached age 45 by the end of the observation period (data not shown); however, the OR for childhood autism associated with being second-born was somewhat attenuated at 1.35 (95% CI, [0.92, 1.97]).

Comment

This study examined the association between maternal parity and ASD diagnoses in a large national birth cohort. Several findings were noted. First, risk of combined ASDs decreased with increasing parity; however risk of childhood autism was highest among second-born children. Second, the associations were not due to confounding by sibship size. Third, no evidence for significant differences in the parity-autism association by sibship size was found.

In contrast to our finding of greatest risk for childhood autism in second-born children, early studies on childhood autism/autistic disorder,^{3, 4, 6, 7, 27} generally found higher risk among children born first or fourth and later in the sibship. Some of these studies also examined variation in the parity-autism association by sibship size^{3, 7}, but were hampered by small sample sizes and non-population-based subject ascertainment.

Our finding that risk of total ASDs decreased with increasing maternal parity was consistent with recent studies from the U.S.,^{2, 8, 9} Australia,⁵ and Canada.¹⁰ Unlike our finding of highest risk among second-born children for childhood autism, Croen and colleagues reported an OR of 0.83 (CI, 0.73, 0.94) for the association between increasing parity and autistic disorder,⁸ implying highest risk in first-born children. Nonetheless, the differences we observed in parity-ASD associations when examining all ASDs combined versus childhood autism alone suggest separate examination of autism subtypes, or other categories of heterogeneity within the ASD spectrum, when assessing risk factors. We also adjusted for family size, an advantage over previous studies. Finally, it is possible that true differences exist between populations.

Differences in patterns of association between maternal parity and ASD subtypes may indicate variation in relative contributions of genetic and environmental factors to risk. While the validity of these separate diagnostic categories within ASD is questionable,²⁸ ASDs remain heterogeneous in aetiology and symptomatology. This is underscored by our finding of differences between the subtypes. Nonetheless, some factor other than specific diagnostic category likely better accounts for these differences. Comorbid intellectual disability does not appear to be such a factor here, given that the associations described above persisted among the cases not diagnosed with MR. Further investigation of specific symptoms or co-morbidity that may better explain these differences could be a fruitful future direction.

Biological factors may explain some of the associations observed in this study. Maternal exposure to infection has previously been invoked as a possible explanation for autism-parity associations^{3, 4, 6} and may be increased in women with young children, particularly those attending day care.²² Maternal exposure to infection was associated with autism previously,^{29, 30} and elevated maternal C-reactive protein, a biomarker of inflammation, was associated with autism in the FiPS-A.³¹ Thus maternal infection could be one explanation for the increased risk of childhood autism observed in second-born children. It is unclear, however, why autism risk would not also be increased in later children if infection was responsible. Explanations for decreasing risk of ASD with higher parity, observed in this study for Asperger syndrome and PDD-NOS, have previously been discussed.⁹ These include the “hygiene hypothesis” which posits that lack of early infectious disease exposure leads to autoimmune susceptibility. In this case, increased exposure to infection among later-born children is hypothesized to be protective rather than potentially harmful. Earlier pregnancies also have exposure to higher levels of lipophilic chemicals²⁰, some of which have been associated with neurodevelopmental impairments;³² and higher risk of pre-

eclampsia,¹⁵ although the association of pre-eclampsia with ASD has not been definitively determined.³³

Alternatively, variation by parity in ascertainment of ASD may have occurred. While differential access to services is not expected to play a large role in this population, perception of a child's behavioural characteristics may vary depending on the presence of siblings. An epidemiologic study of Asperger syndrome prevalence in Northern Finland found that 47% of 8-year old children identified with the disorder had not been previously diagnosed; some had received alternate diagnoses, while others may not have sought help for their behavioural problems.³⁴ The observed highest risk of Asperger syndrome and PDD-NOS in first-born children may indicate increased treatment seeking or concern about a child's social and communicative abilities among parents lacking experience with prior children. It is possible that this is particularly the case for Asperger syndrome, which is characterized by the preservation of cognitive development and spoken language, whereas the greater levels of impairment present in children diagnosed with childhood autism are likely to prompt attention in nearly all cases.

Unlike childhood autism, children with Asperger syndrome or PDD-NOS were more likely than controls to have no siblings. Although one possible interpretation is that families of a first child with one of these disorders are less likely to have additional children, this seems unlikely given that the pattern did not appear for the most severe ASD diagnosis (childhood autism). Asperger syndrome in particular is diagnosed at later ages, when subsequent siblings are likely to already be born. This study also did not show significant evidence for variation in the parity-ASD association by family size, which would be expected if the birth or diagnosis of a child with ASD altered subsequent childbearing. This does not mean that a disability in one child does not influence parental reproductive decisions; however it may be that because different reactions (i.e. having more vs. fewer children) exist,³⁵ no clear pattern is observed.

Important strengths of this study include the use of sibling information to address confounding and effect modification by sibship size as potential explanations for parity-ASD associations, and the accurate ascertainment of maternal sibships. Additionally, the sample was large and drawn from an entire country, and data on covariates were available, as was information on ASD subtype.

Limitations should be noted. The Asperger syndrome and PDD-NOS register-based diagnoses used have not been validated—however, because in Finland, clinical assessment for any ASD is done through specialized services,³⁶ specificity of these register diagnoses is expected to be high. Nonetheless, differential sensitivity of diagnosis remains one possible explanation for observed associations. Finally, the phenomena explored here—including maternal exposures related to parity, characteristics associated with family size, and impact of a child's disability on additional childbearing—may be population-specific. Whether factors such as maternal infection or exposure to environmental chemicals vary by maternal parity in this population or to what extent they may explain the associations observed here was beyond the scope of the current study.

In conclusion, we observed differences in patterns of association between maternal parity and ASD subtypes, with second-born children at greatest risk of childhood autism, and first-born children at greatest risk of PDD-NOS and Asperger syndrome. Additional research will be required to determine whether this indicates contributions of different aspects of the foetal environment to risk, or differences in ascertainment depending on position in the family.

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Table 1

Distribution of characteristics for subjects with ASD diagnoses and matched controls, by diagnostic sub-type, among Finnish births between 1987–2005.

Characteristic	All ASDs		Childhood autism		Asperger syndrome		PDD-NOS	
	Cases, % (N=4704)	Controls, % (N=18,738)	Cases, % (N=1130)	Controls, % (N=4507)	Cases, % (N=1783)	Controls, % (N=7104)	Cases, % (N=1791)	Controls, % (N=7127)
Sibship size								
1	12.5	8.5*	8.9	8.5	13.0	8.6*	14.4	8.5*
2	38.8	38.8	39.6	38.7	41.1	38.5	36.1	39.1
3	28.4	30.7	31.7	29.7	27.8	30.8	27.0	31.2
4+	20.2	22.0	19.9	23.1	18.1	22.1	22.6	21.2
Maternal age								
15–19	2.4	1.8*	1.3	2.3*	1.7	1.7*	3.7	1.6*
20–24	15.2	15.3	14.0	15.2	13.9	15.8	17.3	14.9
25–29	31.9	35.2	32.0	34.3	34.7	35.9	29.0	35.0
30–34	29.5	30.4	30.6	30.3	28.5	29.9	29.8	31.0
35–39	16.5	14.1	17.8	14.9	17.1	13.6	15.0	14.0
40+	4.6	3.2	4.3	3.0	4.2	3.1	5.2	3.5
Paternal age ^a								
15–19	0.6	0.5*	0.2	0.7*	0.4	0.4*	1.1	0.5*
20–24	8.2	7.9	7.6	8.3	7.1	7.9	9.7	7.7
25–29	26.1	28.0	23.5	26.9	29.1	28.9	24.8	27.7
30–34	32.2	33.8	32.3	33.9	32.9	33.9	31.5	33.6
35–39	19.6	19.6	22.7	19.8	17.6	19.0	19.7	20.0
40–49	12.1	9.4	12.2	9.6	12.0	9.0	12.0	9.7
50+	1.2	0.8	1.6	0.7	0.9	0.8	1.2	0.7
Maternal smoking during pregnancy ^a	17.3	15.9*	17.1	16.8	13.6	15.6*	21.1	15.8*
Maternal psychiatric diagnosis	10.9	5.5*	8.0	5.1*	9.2	5.9*	14.4	5.4*
Paternal psychiatric diagnosis ^a	12.7	7.9*	10.4	7.9*	11.2	8.2*	15.6	7.7*

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* p-value <0.05 for difference between cases and controls across all variable categories, among observations with non-missing data, using χ^2 test or Fisher's exact test for tables with cell counts <5.

^aData were missing for the following numbers of observations: *paternal age* and *paternal psychiatric diagnosis*: childhood autism, 20 cases and 42 controls; Asperger syndrome, 39 cases and 91 controls; PDD-NOS, 46 cases and 85 controls; *maternal smoking during pregnancy*: childhood autism, 47 cases and 132 controls; Asperger syndrome, 48 cases and 155 controls; PDD-NOS, 50 cases and 169 controls.

Associations of maternal parity and autism spectrum disorders among children with ASDs and matched controls from Finnish births between 1987–2005.

Table 2

Parity	Controls	Cases	Unadjusted		Adjusted for sibship size		Adjusted for all covariates ^a	
			OR	95% CI	OR	95% CI	OR	95% CI
All ASDs								
Childhood autism								
	%, <u>n=17,130</u>	%, <u>n=4459</u>						
0	40.7	48.1	1.00	Reference	1.00	Reference	1.00	Reference
1	34.5	32.1	0.79	[0.73, 0.85]	0.84	[0.77, 0.91]	0.74	[0.68, 0.80]
2	16.3	13.0	0.67	[0.61, 0.75]	0.71	[0.63, 0.79]	0.53	[0.47, 0.61]
3+	8.5	6.9	0.68	[0.60, 0.78]	0.69	[0.59, 0.81]	0.43	[0.35, 0.51]
	%, <u>n=4086</u>	%, <u>n=1065</u>						
0	40.8	33.5	1.00	Reference	1.00	Reference	1.00	Reference
1	33.1	42.4	1.55	[1.33, 1.81]	1.68	[1.42, 1.99]	1.51	[1.27, 1.81]
2	16.2	16.2	1.22	[0.99, 1.49]	1.33	[1.05, 1.68]	1.03	[0.80, 1.37]
3+	9.9	7.8	0.96	[0.73, 1.24]	1.17	[0.84, 1.63]	0.80	[0.55, 1.17]
Asperger syndrome								
	%, <u>n=6517</u>	%, <u>n=1696</u>						
0	41.2	59.6	1.00	Reference	1.00	Reference	1.00	Reference
1	34.4	25.4	0.51	[0.45, 0.58]	0.52	[0.46, 0.59]	0.42	[0.36, 0.48]
2	16.2	11.0	0.46	[0.39, 0.55]	0.47	[0.39, 0.57]	0.29	[0.23, 0.36]
3+	8.2	4.1	0.34	[0.26, 0.44]	0.32	[0.24, 0.43]	0.14	[0.10, 0.19]
PDD-NOS								
	%, <u>n=6527</u>	%, <u>n=1698</u>						
0	40.2	45.7	1.00	Reference	1.00	Reference	1.00	Reference
1	35.4	32.3	0.81	[0.71, 0.91]	0.91	[0.80, 1.04]	0.85	[0.74, 0.98]
2	16.5	13.0	0.69	[0.58, 0.81]	0.76	[0.63, 0.92]	0.65	[0.53, 0.81]
3+	7.92	9.0	1.00	[0.82, 1.22]	0.99	[0.78, 1.27]	0.76	[0.57, 1.03]

^a Sibship size, maternal and paternal ages, maternal smoking during pregnancy, and maternal and paternal psychiatric diagnoses.

Bold values indicate $p < 0.05$

Associations of maternal parity and autism spectrum disorders among children with ASDs and matched controls from Finnish births between 1987–2005, stratified by presence or absence of mental retardation in the cases. Stratified analyses were not conducted for Asperger syndrome due to the low number of cases with MR.

Table 3

Parity	OR ^a	95% CI	OR ^a	95% CI
All ASDs				
Cases with MR (n=571)		Cases without MR (n=3888)		
0	1.00	Reference	1.00	Reference
1	1.20	[0.93, 1.54]	0.69	[0.63, 0.76]
2	0.87	[0.61, 1.26]	0.50	[0.44, 0.58]
3+	0.73	[0.44, 1.22]	0.40	[0.32, 0.48]
Childhood Autism				
Cases with MR (n=308)		Cases without MR (n=757)		
0	1.00	Reference	1.00	Reference
1	1.36	[0.96, 1.94]	1.58	[1.28, 1.94]
2	1.38	[0.84, 2.28]	0.93	[0.67, 1.28]
3+	0.86	[0.43, 1.72]	0.77	[0.48, 1.21]
PDD-NOS				
Cases with MR (n=240)		Cases without MR (n=1458)		
0	1.00	Reference	1.00	Reference
1	1.23	[0.84, 1.80]	0.80	[0.69, 0.93]
2	0.56	[0.31, 1.02]	0.67	[0.54, 0.84]
3+	0.57	[0.25, 1.31]	0.81	[0.59, 1.10]

^a Odds ratios for parity adjusted for sibship size, maternal and paternal ages, maternal smoking during pregnancy, and maternal and paternal psychiatric diagnoses. Bold values indicate p<0.05