

Supplement 1

Patient-Sibling Analysis

An association between interpregnancy interval (IPI) and autism spectrum disorder (ASD) may potentially be confounded by family-level factors. If traits or exposures at the level of the family, rather than the individual, are responsible for an IPI-ASD association, then all siblings born in a family with a given IPI should equally be at increased risk. If exposures related to the given IPI itself confer the increased risk, then the individual born following that IPI should be specifically at increased risk relative to his or her siblings. We therefore conducted a supplementary patient-sibling control analysis. The population for this analysis consisted of 2,862 matched pairs of patients with ASD and their unaffected siblings who constituted the first- and second-born children to a given mother and father. Only first- and second-born children were included in this analysis in order to clearly differentiate between the siblings whose prenatal experiences were, versus were not, potentially impacted by the IPI.

Interbirth interval (IBI; calculated as the difference in birth dates between two siblings) was used as an estimate of IPI due to missing information on gestational age of siblings. To achieve categories roughly equivalent to those used for the IPI analyses, 9 months were added to each cutpoint (i.e. $IBI < 21$ months was substituted for $IPI < 12$ months).

Conditional logistic regression models were used to test whether the association of ASD with birth order (first- or second-born within the sibship) was modified by IBI. This was accomplished by including terms for birth order and for birth order x IBI products in models. Models were fit, which were unadjusted; and adjusted for potential confounders that vary between children in the same family: maternal and paternal ages (categorized as in the primary analysis), birth year (categorized roughly into quartiles: 1990 and earlier, 1991-1993, 1994-1997, and 1998 and later), and child sex.

Table S1. Frequencies of Covariates by Interpregnancy Interval (IPI) Among Singleton, Non-Firstborn Controls From Finnish Births, 1987-2005.

	IPI (months)					Chisquare <i>p</i> -value
	<12	12-23	24-59	60-119	>=120	
<i>Maternal age</i>						
15-24	20.3	11.5	6.2	1.9	0	<.001
25-29	39	38.5	31.2	17.4	0.9	
30-34	29.3	34.3	41.7	41.4	22.7	
35-39	9.1	12.9	17.4	33.3	50.9	
40+	2.4	2.8	3.5	6	25.6	
<i>Paternal age</i>						
15-24	10.6	4.1	2.1	1.5	1.3	<.001
25-29	33.9	27.6	18.2	11.6	4.3	
30-34	31.5	38.2	42.7	27	19.3	
35-39	16.1	20.2	26	38.9	33.5	
40-49	7.3	9	10.4	20.4	37.3	
50+	0.7	0.9	0.7	0.7	4.3	
Parental psychiatric disorder	12.1	11.4	11.8	16.3	17.6	.001
Maternal parity, 2+ (referent=1)	36.3	32.9	45.3	51.8	46.6	<.001
History of miscarriage/abortion	25.9	27.4	29.5	34.1	32.9	.001
ASD diagnosis in any prior sibling	0.3	0.7	0.4	0.1	0.4	.31
<i>Maternal SES</i>						
Upper white collar	13.6	17.2	17.5	13.2	12.5	<.001
Lower white collar	42.1	42.3	46.2	48.8	47.7	
Blue collar	19.2	18.9	19.7	27.2	30.1	
Other	25.1	21.6	16.6	10.8	9.7	
Preterm birth	3.4	3.1	3.6	5.7	8.2	<.001
Low birth weight	1.5	1.5	1.4	3.8	5.2	<.001

Note: ASD = autism spectrum disorder; SES = socioeconomic status.

Table S2. Sensitivity Analyses for the Association Between Interpregnancy Interval (IPI) and Autism Spectrum Disorders (ASD) in Finnish Births, 1987-2005.

	Adjusted for LBW and PTB ^a			Adjusted for maternal SES ^b			No prior maternal abortion ^c			No prior ASD diagnosis in sibling ^d		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
IPI (months)												
<12	1.52	(1.31,	1.76)	1.56	(1.30	1.86)	1.62	(1.33	1.97)	1.47	(1.26	1.71)
12-23	1.16	(1.01,	1.33)	1.17	(1.00	1.38)	1.17	(0.98	1.41)	1.13	(0.98	1.30)
24-59	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
60-119	1.26	(1.06,	1.49)	1.33	(1.09	1.62)	1.44	(1.14	1.82)	1.28	(1.08	1.51)
>=120	1.37	(1.07,	1.75)	1.42	(1.05	1.92)	1.54	(1.09	2.18)	1.46	(1.13	1.88)

Note: all column data odds ratios adjusted for maternal age, paternal age, parental psychiatric disorders, parity, previous miscarriage/abortions, any ASD diagnosis in a prior sibling. LBW = low birth weight; PTB = preterm birth; SES = socioeconomic status.

^a Odds ratio also adjusted for low birth weight and preterm birth.

^b Odds ratio also adjusted for maternal socioeconomic status.

^c Analysis restricted to observations where no prior maternal abortion (spontaneous or induced) was recorded.

^d Analysis restricted to observations where no prior sibling had an ASD diagnosis.

^e Parental age adjustment conducted using continuous (linear) terms for maternal and paternal ages.

Table S3. Results of a Regression Model for the Association Between Autism Spectrum Disorders and Second Versus First Birth Order Within the Sibship, Including Product Terms for Birth Order x Interbirth Interval (IBI), Among 2,862 Discordant First and Second-Born Sibling Pairs.

	Sibling pairs (n)		Unadjusted		Adjusted ^a	
	1 st affected	2 nd affected	OR	p	OR	p
<i>Second born (Referent=first born)</i>	--	--	0.79	.00	0.85	.19
<i>Second born x IBI^b</i>						
<21 months	329	328	1.27	.02	1.23	.12
21-32 months	562	407	0.92	.37	0.87	.22
33-68 months (Ref)	476	375	1.00	Ref	1.00	Ref
69-128 months	135	156	1.47	.01	1.39	.08
>=129 months	20	74	4.70	<.0001	3.64	.00

Note: Ref = reference category.

^a Adjusted for: maternal and paternal ages, birth year, child sex.

^b Interbirth interval corresponds to approximately IPI + 9 months