Interpregnancy Interval and Risk of Autistic Disorder

Nina Gunnes,[a] *Pål Surén,*[a] *Michaeline Bresnahan,*[b,c] *Mady Hornig,*[b,d] *Kari Kveim Lie,*[a] *W. Ian Lipkin,*[b,d] *Per Magnus,*[a] *Roy Miodini Nilsen,*[e,f] *Ted Reichborn-Kjennerud,*[a,g] *Synnve Schjølberg,*[a] *Ezra Saul Susser,*[b,c] *Anne-Siri Øyen,*[a,h] *and Camilla Stoltenberg*[a,e]

Background: A recent California study reported increased risk of autistic disorder in children conceived within a year after the birth of a sibling.

Methods: We assessed the association between interpregnancy interval and risk of autistic disorder using nationwide registry data on pairs of singleton full siblings born in Norway. We defined interpregnancy interval as the time from birth of the first-born child to conception of the second-born child in a sibship. The outcome of interest was autistic disorder in the second-born child. Analyses were restricted to sibships in which the second-born child was born in 1990–2004. Odds ratios (ORs) were estimated by fitting ordinary logistic models and logistic generalized additive models.

Results: The study sample included 223,476 singleton full-sibling pairs. In sibships with interpregnancy intervals <9 months, 0.25% of the second-born children had autistic disorder, compared with 0.13% in the reference category (≥36 months). For interpregnancy intervals shorter than 9 months, the adjusted OR of autistic disorder in the second-born child was 2.18 (95% confidence interval 1.42–3.26). The risk of autistic disorder in the second-born child was also increased for interpregnancy intervals of 9–11 months in the adjusted analysis (OR = 1.71 [95% CI = 1.07–2.64]).

Conclusions: Consistent with a previous report from California, interpregnancy intervals shorter than 1 year were associated with increased risk of autistic disorder in the second-born child. A possible explanation is depletion of micronutrients in mothers with closely spaced pregnancies.

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The interpregnancy interval is defined as the time between one pregnancy and the next for an individual woman. Several studies have found associations between short interpregnancy intervals and adverse pregnancy outcomes in the later-born child, such as preterm birth, low birth weight, and small size for gestational age.[1–5] However, findings are not consistent across studies. Other studies have failed to demonstrate associations between short interpregnancy intervals and outcomes such as intrauterine growth restriction and prematurity.[6,7]

A recent study from California found that closely spaced pregnancies were associated with increased risk of autistic disorder in the later-born child, with the largest increase observed for pregnancies spaced less than 1 year apart.[8] Similar findings have been reported for schizophrenia. A registry-based study from Sweden found that the risk of schizophrenia was elevated in children conceived after interpregnancy intervals of 6 months or shorter,[9] and another registry-based study from Denmark showed increased risk of schizophrenia in the later-born child for interbirth intervals of 26 months or shorter (roughly corresponding to interpregnancy intervals ≤17 months).[10] Although the etiologic mechanisms of autism spectrum disorder (ASD) and schizophrenia are diverse and not fully understood, findings from molecular genetic studies indicate an etiologic overlap between the two disorders.[11] Advanced paternal age is a common risk factor for both ASD and schizophrenia and may be mediated by a higher frequency of de novo gene mutations in children of older fathers.[12–15]

It has been hypothesized that unfavorable outcomes associated with short interpregnancy intervals are caused by deficiencies in essential micronutrients in early pregnancy. Mothers may be depleted of micronutrients during pregnancy and postpartum, and it may take several months to restore nutritional status after delivery.[16]

We assessed the association between interval from birth of the first-born child to conception of the second-born child and risk of autistic disorder in the second-born child. Analyses

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From the [a]Norwegian Institute of Public Health, Oslo, Norway; [b]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; [c]New York State Psychiatric Institute, New York, NY; [d]Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, NY; [e]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [f]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; [g]Institute of Psychiatry, University of Oslo, Oslo, Norway; and [h]Nic Waals Institute, Lovisenberg Diakonale Hospital, Oslo, Norway.

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Correspondence: Nina Gunnes, Norwegian Institute of Public Health, P.O. Box 4404 Nydalen, N-0403 Oslo, Norway. E-mail: Nina.Gunnes@fhi.no.

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were based on Norwegian nationwide registry data on singleton full siblings (first- and second-born children).

METHODS

Data were derived from two Norwegian registries with complete population coverage: the Medical Birth Registry of Norway and the Norwegian Patient Registry. Additional socioeconomic information was obtained from Statistics Norway. Linkage between the data sources was based on the unique (encrypted) personal identification number assigned to each resident of Norway in the National Population Registry.

The birth registry was established in 1967 and contains data on all pregnancies lasting 12 weeks or longer (16 weeks or longer before 2001). Reporting is mandated by law. A standardized notification form is used to report essential information about the pregnancy and delivery, including demographic information, maternal reproductive history and health before and during pregnancy, pregnancy and birth complications, and pregnancy outcomes.

The patient registry is an administrative database containing activity data from all Norwegian government-owned hospitals and outpatient clinics.[17] Reporting is mandatory and linked to the governmental reimbursement system for funding of health services. Diagnoses are reported as International Classification of Diseases, Tenth Edition (ICD-10) codes. Individual-level research data are available from 2008 onwards.

Variables

Information was obtained about all ASD diagnoses recorded in the patient registry from 2008 through 2010. Diagnoses of ASD have previously been validated through in-person clinical assessments of the Autism Birth Cohort Study, a case-cohort study of ASD nested within the population-based Norwegian Mother and Child Cohort Study.[18] The ASD diagnoses from the case-cohort study are based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). The validity of ASD diagnoses in the patient registry is high; of 60 registry ASD cases assessed through the case-cohort study, 58 were found to meet the DSM-IV-TR criteria for ASD, generating a positive predictive value of 97% (95% confidence interval [CI] = 88%–100%). Positive predictive value was also high for the specific diagnosis of autistic disorder, 85% (17/20) (95% CI = 62%–97%), but lower for the other two ASD subtypes, Asperger's disorder (36% [8/22]; 95% CI = 17%–59%) and pervasive developmental disorder not otherwise specified (PDD-NOS) (56% [10/18]; 95% CI = 31%–78%). Estimates for the positive predictive value of the subtype diagnoses should be interpreted with caution, as the number of cases in each group was low.

The following ICD-10 codes were included in the ASD case definition: F84.0 ("childhood autism"), F84.1 ("atypical autism"), F84.5 ("Asperger's syndrome"), F84.8 ("other pervasive developmental disorders"), and F84.9 ("pervasive developmental disorder, unspecified"). Persons with ICD-10 code F84.2 ("Rett's syndrome") or ICD-10 code F84.3 ("other childhood disintegrative disorder") were not classified as ASD cases of any kind, regardless of the presence of other relevant ICD-10 codes. The DSM-IV-TR terms for diagnoses are used throughout the text; autistic disorder corresponds to ICD-10 code F84.0, Asperger's disorder corresponds to ICD-10 code F84.5, and PDD-NOS corresponds to any of the ICD-10 codes F84.1, F84.8, and F84.9.

In order to replicate the California study,[8] autistic disorder in the second-born child was chosen as the primary outcome. We also conducted supplementary analyses in which the other two ASD subtypes (Asperger's disorder and PDD-NOS) and ASD (ie, the entire autism spectrum) in the second-born child were used as outcomes.

Interpregnancy interval was calculated as time from date of birth of the first-born child to date of conception (date of birth minus length of gestation) of the second-born child, as recorded by the birth registry. Length of gestation was based on information from ultrasound scanning whenever this was available; otherwise, the first day of the last menstrual period was used. The interpregnancy interval was then rounded down to whole months and categorized as follows: <9 months, 9–11 months, 12–23 months, 24–35 months, and ≥36 months. Interpregnancy intervals shorter than 9 months comprised mostly intervals of 6–8 months.

Based partly on the previous literature and partly on associations observed with both the outcome and the exposure, the following variables linked to the second-born child were selected as covariates: sex (girl or boy), year of birth (1990–1992, 1993–1995, 1996–1998, 1999–2001, or 2002–2004), maternal age at delivery (<25 years, 25–29 years, 30–34 years, or ≥35 years), paternal age at delivery (<25 years, 25–29 years, 30–34 years, 35–39 years, or ≥40 years), and maternal education in the year of delivery (less than secondary school; secondary school or above, but not university/college; or university/college). Information about sex, year of birth, and parental age was obtained from the birth registry; information about maternal education was obtained from Statistics Norway.

Study Sample

All records in the merged data file lacking values for the personal identification number of the child, the mother, or the father were discarded. Full siblings were identified by matching the personal identification numbers of the parents. The study sample was restricted to pairs of singleton full siblings with maternal parity of 0 or 1, in which the second sibling was born during 1990–2004. Sibling pairs in which the second-born child was born before 1990 were not included because the proportions with ASD were low, indicating a substantial under-ascertainment of ASD. Children born after 2004 were also omitted because most ASD cases among those children

were still too young to have been registered with a diagnosis by the end of follow-up in 2010. A total of 248,370 sibling pairs were initially eligible for analysis.

We excluded sibling pairs with missing data on interpregnancy interval due to missing information about length of gestation of the second-born child (n = 14,330), sibling pairs wherein one or both of the siblings died within the first 3 years of life (n = 6,124), and sibling pairs wherein the first-born child was registered with ASD (n = 1,392). We excluded sibling pairs with ASD in the oldest child because this diagnosis is likely to be associated with both the mother's subsequent childbearing and ASD risk in the younger sibling. Among the excluded sibling pairs with ASD in the first-born child, 52 of the second-born children were diagnosed with ASD (13 with autistic disorder and 39 with other ASD). Sibling pairs with missing data on any of the covariates (n = 4,373) were also excluded.

A total of 24,894 (10%) eligible sibling pairs were excluded, leaving 223,476 singleton full-sibling pairs. Table 1 displays baseline characteristics of the second-born children in the study sample, by diagnostic status of autistic disorder. These characteristics are also displayed separately for second-born girls (n = 108,883) and second-born boys (n = 114,593) in eTables 1 and 2 (http://links.lww.com/EDE/A721), respectively.

TABLE 1. Baseline Characteristics of the Second-Born Children in the Study Sample, by Autistic Disorder Status (Diagnosed vs. Not Diagnosed)

	Autistic Disorder					
	Yes (n = 303)			No (n = 223,173)		
		Percentage			Percentage	
Characteristic	Number	Column	Row	Number	Column	Row
Sex						
Girl	61	20	0.06	108,822	49	99.94
Boy	242	80	0.21	114,351	51	99.79
Year of birth						
1990–1992	43	14	0.10	44,769	20	99.90
1993–1995	50	17	0.11	44,967	20	99.89
1996–1998	69	23	0.16	44,404	20	99.84
1999–2001	73	24	0.16	45,700	20	99.84
2002–2004	68	22	0.16	43,333	19	99.84
Maternal age (years)						
<25	33	11	0.10	31,531	14	99.90
25–29	129	43	0.14	92,607	41	99.86
30–34	101	33	0.13	76,233	34	99.87
≥35	40	13	0.18	22,802	10	99.82
Paternal age (years)						
<25	16	5	0.16	10,204	5	99.84
25–29	74	24	0.12	64,020	29	99.88
30–34	109	36	0.12	90,024	40	99.88
35–39	73	24	0.17	42,383	19	99.83
≥40	31	10	0.19	16,542	7	99.81
Maternal education						
Less than secondary school	122	40	0.18	69,409	31	99.82
Secondary school or above, but not university or college	87	29	0.12	71,023	32	99.88
University/college	94	31	0.11	82,741	37	99.89
Interpregnancy interval (months)						
<9	33	11	0.25	13,361	6	99.75
9–11	26	9	0.19	13,743	6	99.81
12–23	89	29	0.12	74,547	33	99.88
24–35	70	23	0.12	56,885	25	99.88
≥36[d]	85	28	0.13	64,637	29	99.87

Frequencies based on 223,476 second-born children from pairs of singleton full siblings born in Norway, where the first-born child was not registered with a diagnosis of ASD, the second-born child was born in 1990–2004, and there were no missing values of the main exposure or covariates.

Statistical Analysis

Two types of regression models were used for statistical analysis: the ordinary logistic model and the logistic generalized additive model (GAM).[19,20] GAM regression allows for nonlinear predictor effects using function smoothers, such as splines (smooth, piecewise polynomial functions), and is therefore a highly flexible procedure. Different types of splines and other function smoothers are discussed by Hastie et al.[21]

We used ordinary logistic regression analyses to estimate crude and adjusted odds ratios (ORs) of autistic disorder in the second-born child for each of the interpregnancy interval categories, using the longest interval (≥36 months) as the reference. In fitting the logistic GAMs, the OR scale was centered around and set to 1 on the mean population odds estimated from the specific models. We used the thin-plate regression spline (the default smoother in R) with four degrees of freedom to estimate the effect of interpregnancy interval, which was included in the models as a continuous term measured in whole months. Crude and adjusted ORs of autistic disorder in the second-born child, with associated 95% CIs, were plotted against interpregnancy interval.

We carried out supplementary analyses for all analyses by stratifying the study sample by sex of the second-born child. Separate models for same-sex sibships were also fitted. Potential interaction between sex of the second-born child and interpregnancy interval was explored by adding interaction terms to the ordinary logistic model. These terms were products of the indicator variable for male sex and the indicator variables for the various (nonreference) categories of interpregnancy interval.

The selected covariates were included in the regression models using categorical terms. In a supplementary analysis, the indicator variable for preterm birth of the first-born child was also included.

Data were merged and analyzed using the statistical tools PASW Statistics 17 for Windows (SPSS Inc., Chicago, IL) and R 2.15.0 for Windows (The R Project for Statistical Computing).

RESULTS

A total of 966 (0.43%) of the 223,476 second-born children in the study sample had been diagnosed with ASD; 303 (0.14%) had autistic disorder, 426 (0.19%) had Asperger's disorder, and 237 (0.11%) had PDD-NOS. Interpregnancy interval was distributed as follows: 13,394 (6%) shorter than 9 months, 13,769 (6%) 9–11 months, 74,636 (33%) 12–23 months, 56,955 (25%) 24–35 months, and 64,722 (29%) 36 months or longer. The mean interpregnancy interval was 31 months, and the median interpregnancy interval was 25 months. Of the second-born children with interpregnancy intervals <9 months, 0.25% (33/13,394) had autistic disorder, compared with 0.13% (85/64,722) of the second-born children in the reference category (≥36 months).

Results from the main ordinary logistic regression analyses, with autistic disorder as the outcome, are displayed in Table 2. In the crude analysis, interpregnancy intervals shorter than 9 months were associated with increased risk of autistic disorder (OR = 1.88 [95% CI = 1.24–2.78]). This association was strengthened in the adjusted analysis (2.18 [1.42–3.26]). Interpregnancy intervals of 9–11 months were also associated with increased risk of autistic disorder (crude OR = 1.44 [0.91–2.20]; adjusted OR = 1.71 [1.07–2.64]). Results from supplementary analyses of Asperger's disorder and PDD-NOS (combined into one outcome variable) and of ASD as a whole are provided in eTables 3 and 4 (http://links.lww.com/EDE/A721). Although Asperger's disorder and PDD-NOS comprise the majority of ASDs, there was no evidence to support a higher risk of those subtypes for the shortest interpregnancy intervals (<9 months) (crude OR = 0.82 [0.57–1.15]; adjusted OR = 0.85 [0.59–1.20]), nor was there an overall pattern suggesting any association with interval.

Preterm birth of the older sibling might affect the interpregnancy interval and also share antecedents with autistic disorder in the younger sibling. Additional adjustment for preterm birth of the first-born child, however, had little impact on the results; the adjusted OR of autistic disorder in the

TABLE 2. OR of Autistic Disorder in the Second-Born Children, with Associated 95% CI

	Autistic Disorder		Crude Analysis[a]		Adjusted Analysis[b,c]	
Interpregnancy Interval (Months)	Yes (n = 303) No.	No (n = 223,173) No.	OR	(95% CI)	OR	(95% CI)
<9	33	13,361	1.88	(1.24–2.78)	2.18	(1.42–3.26)
9–11	26	13,743	1.44	(0.91–2.20)	1.71	(1.07–2.64)
12–23	89	74,547	0.91	(0.67–1.22)	1.07	(0.78–1.45)
24–35	70	56,885	0.94	(0.68–1.28)	1.06	(0.77–1.47)
≥36[d]	85	64,637	1.00		1.00	

Frequencies and analyses based on 223,476 second-born children from pairs of singleton full siblings born in Norway, where the first-born child was not registered with a diagnosis of ASD, the second-born child was born in 1990–2004, and there were no missing values of the main exposure or covariates.

[a]Test for trend (including the ordered categorical main exposure as a linear term): P value = 0.01.

[b]Adjusted for sex, year of birth, maternal age, paternal age, and maternal education.

[c]Test for trend (including the ordered categorical main exposure as a linear term): P value < 0.01.

[d]Reference category.

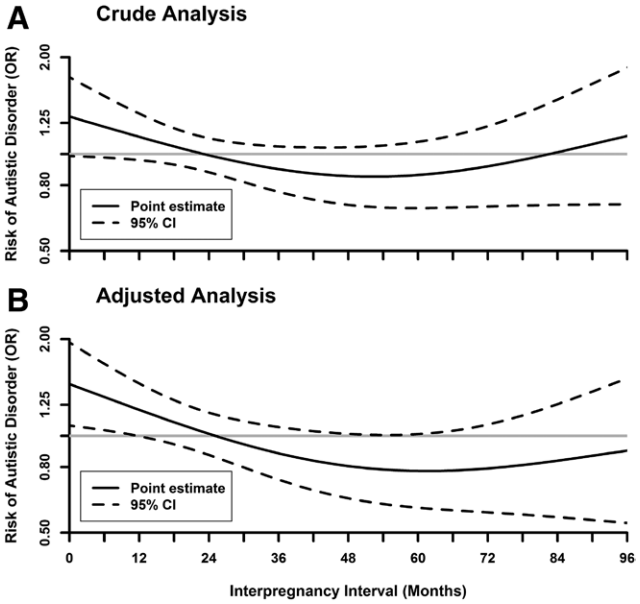

FIGURE. OR of autistic disorder in the second-born children, with associated 95% CI, as a function of interpregnancy interval. The analyses were based on 223,476 second-born children from pairs of singleton full siblings born in Norway, where the first-born child was not registered with a diagnosis of ASD, the second-born child was born in 1990–2004, and there were no missing values of the exposure or covariates. The analyses were performed both (A) crude and (B) with adjustment for sex, year of birth, maternal age, paternal age, and maternal education.

second-born children for interpregnancy intervals <9 months went from 2.18 (1.42–3.26) to 2.39 (1.54–3.64), whereas the other adjusted ORs remained largely unchanged (eTable 5, http://links.lww.com/EDE/A721).

Sex-stratified analyses and analyses restricted to same-sex sibships did not reveal any obvious sex differences (eTables 6–9, http://links.lww.com/EDE/A721). This was confirmed by testing the interaction between sex and interpregnancy interval using the likelihood ratio test of nested models (P value = 0.79). However, the small number of girls with autistic disorder limited the statistical power of these subanalyses.

The Figure displays smoothed dose–response curves obtained from the fitted logistic GAMs, with the crude and adjusted ORs of autistic disorder in the second-born children plotted against interpregnancy interval (in whole months). As with the ordinary logistic regression analysis, adjustment for potential confounding strengthened the association with interpregnancy interval.

DISCUSSION

Interpregnancy intervals shorter than 12 months were associated with increased risk of autistic disorder in the second-born child, compared with intervals of 36 months or longer. The increase in risk was larger for intervals <9 months than for intervals of 9–11 months. These findings are consistent with the previous findings from California,[8] although the association here was somewhat weaker.

Interpregnancy intervals shorter than 6 months could not be analyzed as a separate exposure category due to small numbers. Almost all children in Norway are breastfed, and breast milk is usually the main source of calories during the first half-year of life. Breastfeeding limits the number of interpregnancy intervals <6 months as it suppresses ovulation and reduces fertility.[22] About two-thirds of interpregnancy intervals <9 months in the study sample lasted 6–8 months. This suggests that the most extreme risk associated with the shortest interpregnancy intervals might not have been fully captured. If the association of interpregnancy interval with autistic disorder is related to maternal nutritional depletion, then intervals shorter than 6 months are likely to be associated with more severe depletion of micronutrients. On the other hand, the nutritional burden on the mother between two successive pregnancies also depends on the extent of breastfeeding,[23] so this may not have represented a substantial limitation.

There is substantial evidence of associations between poor maternal nutrition and brain development in the offspring. In studies of persons exposed in utero to the Dutch famine of 1944–1945, maternal starvation during pregnancy was associated with increased risk of schizophrenia in later life.[24,25] The risk of schizophrenia was also increased in persons prenatally exposed to the Chinese famine of 1959–1961.[26]

Maternal deficiencies of folate (vitamin B9) may be of particular importance with respect to unfavorable pregnancy outcomes.[16,27] Recent studies indicate that maternal folic acid supplementation in early pregnancy may prevent neurodevelopmental disorders in children.[28–31] A study from California found decreased risk of autistic disorder in children whose mothers had used prenatal vitamin supplements containing folic acid.[28] Studies based on a Norwegian child cohort showed that maternal use of folic acid in early pregnancy was associated with decreased risk of both severe language delay and autistic disorder in the offspring.[29,30]

Information about maternal use of folic acid supplements before and during pregnancy is available in the Norwegian birth registry, but only for children born in 1999 or later. Even then, folate use is substantially underreported.[30] With these limitations in mind, we considered the potential interaction between maternal folate use and interpregnancy interval for children born in 1999 or later. The effect of short interpregnancy intervals appeared to be stronger in children whose mothers had not used folate before or during pregnancy, although this interaction was far from statistically significant (P value = 0.88). Larger studies with more precise measures of folic acid use are required to determine whether the risk associated with short interpregnancy intervals is modified by maternal use of folic acid supplements.

Although maternal folate depletion is a plausible explanation of the association between short interpregnancy intervals and increased risk of autistic disorder, other factors may also play a role. Closely spaced pregnancies may be associated with increased maternal stress during the second pregnancy. In a study from Western Australia, prenatal maternal stress, as measured by exposure to stressful life events during pregnancy, was associated with autistic traits in early childhood.[32] An alternative pathway is through maternal inflammation. There is some evidence of a persistent, systemic inflammatory response in the postpartum period.[33] When conception occurs at relatively short intervals after delivery, it is possible that lingering maternal inflammation may affect fetal development. Elevation of maternal C-reactive protein, an inflammatory biomarker, early in pregnancy was recently found to be associated with increased risk of autistic disorder in offspring.[34] Also, residual confounding by socioeconomic factors, for example, factors related to decisions about child spacing and use of effective birth control, remains possible. Further research is needed to shed more light on these additional factors.

Supplementary analyses of the other two ASD subtypes (Asperger's disorder and PDD-NOS) combined did not provide any evidence of increased risk associated with short interpregnancy intervals. Given the large numbers of these subtypes, our data suggest that any effect of interpregnancy interval is restricted to autistic disorder only.

The pattern in the Figure suggests the possibility of a U-shaped relation between interpregnancy interval and risk of autistic disorder, with increased risk for both short intervals and long intervals. There are several possible explanations as to why long interpregnancy intervals may also be associated with an increase in risk. One is that reduced fertility and neurodevelopmental disorders in the offspring may share common risk factors. Such factors are often hard to identify. Buchmayer et al[35] suggested difficulties in conceiving as an indirect measure of prenatal infections. In a review, Libbey et al reported on associations between ASD and viral infections, such as congenital rubella virus infection, among others.[36] A U-shaped relation between interpregnancy interval and disease risk would be consistent with studies of other adverse pregnancy outcomes. Previous studies have shown associations between both short and long interpregnancy intervals and higher risk of preterm birth, low birth weight, and small size for gestational age.[2,5]

The magnitude of the association between short interpregnancy intervals and autistic disorder risk was similar in girls and boys. This is in line with the findings from California.[8] However, the proportion of autistic disorder among girls was very low, providing relatively low statistical power. It would be beneficial to include more girls with autistic disorder before concluding that there are no sex differences.

The main strength of the study was the access to registry data with complete population coverage. The sample size was large, even after exclusions. The proportions with missing values were low for all variables, and it is unlikely that the exclusion of records with missing data had a substantial influence on the observed associations.

Exclusion of sibships with ASD in the first-born child did not appear to affect the findings of the study; the results were essentially unchanged after including sibships with ASD in the first-born child. However, it is still possible that the effect of interpregnancy interval may differ between sibships with and without ASD in the first-born child. A simplified post hoc power analysis was conducted to examine whether it would be possible to detect such differences in the study sample, but the statistical power was too low (eAppendix 1, http://links.lww.com/EDE/A721).

Sibling pairs for which the interpregnancy interval could not be determined (due to missing value of length of gestation of the second-born child) were also excluded from the study sample. Missingness of gestational length data could be associated with ASD risk, for instance if missingness was more likely with premature children, who also have increased risk of ASD. A sensitivity analysis was conducted to explore whether these exclusions might have introduced bias (eAppendix 2, http://links.lww.com/EDE/A721). The results from the analysis indicated that exclusion of sibships with missing data on interpregnancy interval did not bias the OR estimates of the study.

The most important limitation of the study was that data on ASD diagnoses were available only from 2008 onwards. This means that if a child was diagnosed with ASD before 2008 and had not been in contact with specialist health services in 2008 or later, the ASD diagnosis would not have been registered. In Norway, most persons with ASD receive regular follow-up from specialist health services.[17] However, high-functioning persons with no need for medical follow-up are usually followed only by local educational services and might not see a medical or mental health specialist very often. Furthermore, it is also likely that some of the youngest children in the study sample had not yet been diagnosed by the end of 2010 due to relevant symptoms not being manifested or diagnostic assessments not being completed at the time. Consequently, there was probably some under-ascertainment of ASD cases in the study sample. However, this is more likely for Asperger's disorder and PDD-NOS than for autistic disorder, which was the outcome of primary interest.

The analyses were based on the first-born child not having been diagnosed with ASD. However, it is conceivable that other disorders in the first-born child, such as neurodevelopmental disorders other than ASD, also could be associated with both interpregnancy interval and risk of autistic disorder in the second-born child. This kind of information was not available. Furthermore, only pregnancies lasting at least 12 weeks (16 weeks before 2001) are registered. This means that women with long interpregnancy intervals might

have had a miscarriage or an abortion without this information being recorded, which could lead to erroneous values of maternal parity. Miscarriages might indicate the presence of underlying medical conditions/disorders in the mother that also have the potential to independently affect the fetus and possibly increase the ASD risk. Elective abortions are often performed because of fetal malformations, which may also be associated with a higher risk of ASD in later-born children. Thus, missing information about miscarriages and abortions could potentially lead to an underestimation of the effect of short interpregnancy intervals on the subsequent risk of autistic disorder.

In conclusion, similar findings from two large epidemiologic studies provide strong evidence of an association between short interpregnancy intervals and increased risk of autistic disorder in the later-born child. Future studies should look into the biological underpinnings of the association, particularly the role of micronutrient depletion in the mother, and also explore whether the association is modified by genetic factors.

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