Increased Risk of Autism Spectrum Disorders at Short and Long Interpregnancy Intervals in Finland

Keely Cheslack-Postava, PhD, Auli Suominen, MSc, Elina Jokiranta, MA, Venla Lehti, MD, Ian W. McKeague, PhD, Andre Sourander, MD, Alan S. Brown, MD

Objective: Both short and long interpregnancy intervals (IPI) are believed to present possible adverse conditions for fetal development. Short IPI has recently been associated with increased risk of autism, but whether long IPI increases risk for autism spectrum disorders (ASD) has not been thoroughly investigated. We investigated the association between short and long IPI in a Finnish population–based study. **Method:** This study was conducted in the Finnish Prenatal Study of Autism, which is based in a national birth cohort. Children born in Finland in 1987 to 2005 and diagnosed with ASD by 2007 were identified through the Finnish Hospital Discharge Register. A total of 2,208 non–firstborn patients with ASD and 5,163 matched controls identified from the Finnish Medical Birth Register were included in the primary analysis. The association between IPI and ASD was determined using conditional logistic regression and adjusted for potential confounders. **Results:** Relative to births with an IPI of 24 to 59 months, those with the shortest IPI (<12 months) had an increased risk of ASD (odds ratio [OR] = 1.50, 95% CI = 1.28, 1.74) in confounder-adjusted models, whereas the ORs for longer IPI births (60–119 months and ≥120 months) were 1.28 (95% CI = 1.08, 1.52) and 1.44 (95% CI = 1.12, 1.85), respectively. **Conclusion:** This study provides evidence that risk of ASD is increased at long as well as short IPI. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(10):1074–1081. **Key Words:** autism spectrum disorders, autism, interpregnancy interval, interbirth interval, birth spacing

Autism spectrum disorders (ASD) are developmental conditions involving impairments in social communication and patterns of restricted interests or repetitive behaviors. The etiology of ASD is believed to stem from a complex combination of genetic and environmental factors.[1] It is generally believed that the prenatal time period is most relevant for the potential impact of nongenetic factors.

Interpregnancy interval (IPI) is a potentially modifiable factor influencing the prenatal environment. Both short and long IPI are believed to present possible adverse conditions for fetal development. Short IPI may result in the depletion of maternal nutrient reserves, in particular, folate,[2] or in conditions of unresolved inflammation from the preceding pregnancy.[3] Longer IPI is associated with increased risk of preeclampsia[4] and has been hypothesized to result in a "physiologic regression" caused by a loss of maternal vascular adaptation from the prior pregnancy.[5] Pregnancies with short or long IPI may also be more likely to be unintended.[6] Unintended pregnancies bear a higher risk of exposure to maternal risk behaviors, including prenatal smoking and alcohol consumption, and inadequate use of prenatal care and folic acid supplementation.[7,8]

An epidemiologic study from California reported an inverse association between IPI less than 36 months and the risk of autism among second-born children.[9] The finding was replicated in a study from Norway, where a 2-fold

This article is discussed in an editorial by Dr. Armin Raznahan on page 1045.

Clinical guidance is available at the end of this article.

Supplemental material cited in this article is available online.

increased risk of autistic disorder was found in pregnancies with IPI less than 9 months.[10] Likewise, a multivariate analysis of obstetric and perinatal factors in children from Nova Scotia, Canada, reported a relative risk for ASD of 1.51 for IPI less than versus more than 18 months.[11] However, it has not yet been determined whether and to what extent this association holds consistently across a variety of different populations. Also, an association between long IPI and increased risk of autistic disorder was suggested graphically by the study from Norway,[10] but this has not yet been tested rigorously.

To test the hypotheses that both short and long IPI are associated with increased risk of ASD, we used data from the Finnish Prenatal Study of Autism (FIPS-A), a population-based patient–control study. In this population, a diagnosis of ASD is facilitated by universal access to health care and regular childhood developmental screenings, and data on participants as well as their parents and siblings are available through linkage of several national registers. A key strength of the present study was the availability of a sufficient number of participants with long IPI (≥60 months).

METHOD

Two sets of analyses were conducted. The primary analysis used non–firstborn patients with ASD and unrelated matched controls and is described in detail below. A complementary patient–sibling analysis addressing the potential for confounding by family-level factors used pairs of first- and second-born siblings in which 1 sibling was diagnosed with ASD. Given the data available, interbirth interval, rather than IPI, served as the exposure variable for the patient–sibling analysis. The selection of participants, definition of exposure, and statistical methods for the patient-sibling analysis are described in detail in Supplement 1, available online.

Data Sources

Patients with ASD and controls were identified through the FIPS-A, a nested patient–control study based on a national birth cohort, which has been described in detail previously.[12] Data in the FIPS-A were linked between registries using unique personal identity codes, which are given at birth to every Finnish resident and remain the same throughout life. The registries used in this study collect and maintain information about Finnish residents and their use of health services. Data used for the current study came from 3 national registries. The Finnish Hospital Discharge Register (FHDR) is maintained by the National Institute of Health and Welfare (THL) and includes all public and private inpatient diagnoses since January 1, 1967, and outpatient diagnoses in specialized public hospital units since January 1, 1998. The Finnish Medical Birth Register (FMBR; also maintained by THL, established in 1987) includes comprehensive data, collected using a standardized form, 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 that contains basic information about Finnish citizens and foreign citizens residing permanently in Finland, including name, personal identity code, address, municipality of residence, citizenship, family relations, and dates of birth and death. 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.

Identification of Participants

Under the recently released *DSM-5*, ASD constitutes a single diagnosis, but it has historically encompassed the related diagnoses of childhood autism or autistic disorder (depending on whether the *DSM* or *International Classification of Diseases [ICD]* is used), Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS). In the FIPS-A, children born in 1987 to 2005 and diagnosed with ASD by the end of 2007 were identified through the FHDR. Diagnoses in the FHDR are based on the *ICD*. *ICD-9* was used from 1987 to 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 as follows: childhood autism (F84.0), Asperger syndrome (F84.5), and other pervasive developmental disorder (PDD) 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 a small number (n = 19) of patients, and their diagnoses were updated to the latest *ICD-10* classifications. A validation study has shown high specificity for the childhood autism diagnosis in the FHDR.[13] Four controls were selected from the FMBR for each patient, matched by date of birth (±30 days), place of birth (birth hospital or regional hospital district), sex, and residence in Finland. The exclusion criteria for population controls were ASD or severe/profound intellectual disability (ID) according to the FHDR.

Selection of patients and controls is illustrated in Figure 1. A total of 5,009 matched sets, comprising 5,009 patients with ASD and 19,956 matched controls, were initially identified. For the current investigation, we excluded participants without any siblings (n = 2,335) and all participants who were firstborn based on maternal parity (n = 8,216), because the exposure of interest, IPI, is not defined for these births. We also