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Birth gap and the recurrence risk of autism spectrum disorders: A population-based cohort study

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ABSTRACT

Population-based data on the magnitude and determinants of Autism Spectrum Disorder (ASD) recurrence risk in families with an index case are rare. We examined whether short birth gaps and other birth spacing factors increase the risk of recurrence, using a population-based cohort study in Israel. We examined records of younger siblings of index cases (children diagnosed with ASD), and estimated recurrence risk and its determinants. Overall, 5.25% (261/4976) of younger siblings were diagnosed with ASD. Younger siblings with birth gaps less than two years of their index case had significantly higher risk compared to the rest (odds ratio = 1.66, 95% CI 1.25–2.22). The association remained significant in models adjusted for sex of the index cases and their younger siblings, ethnicity, parental ages and birth order (odds ratio = 1.43, CI 1.03–1.96). This finding suggests that short birth gaps from the index case increase the risk of ASD among younger siblings.

1. Introduction

Until recently studies of ASD recurrence were based on recruited samples that were of limited size and may not have been population-based (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Jorde, Hasstedt, & Ritvo, 1991; Lauritsen, Jørgensen, & Madsen, 2010; Ozonoff, Young, & Carter, 2011; Ritvo, Jorde, & Mason-Brothers, 1989; Sumi, Tanai, Miyachi, & Tanemura, 2006). They also were mainly concerned with measuring the risk of ASD recurrence rather than testing hypotheses about potential risk factors. The first population-based cohort study of ASD recurrence was for Denmark (Grønborg, Schendel, & Parner, 2013) which found that recurrence risk was 6.9% for full siblings, 2.4% for maternal half-siblings and 1.5% for paternal half-siblings. Subsequently a population-based cohort study for Sweden (Sandin et al., 2014) provided further evidence of the role of kinship and broke new ground by estimating the relationship between recurrence risk and age (4% by 10 years and 12.9% by 20 years). Indeed, the cumulative risk of ASD recurrence, which naturally increases with age, diverges (becomes increasingly larger) rather than converges (levels off) with age. Divergence implies counter-intuitively that children are more likely to be diagnosed with ASD when they are older.

There are numerous possible mechanisms for the development of ASD. It was recently suggested that interpregnancy intervals shorter than one year were associated with increased risk of ASD (Cheslack-Postava, Lui, & Bearman, 2011, Gunnes

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et al., 2013), as well as other adverse health effects such as schizophrenia, and interpregnancy intervals less than six months are associated with preterm births (Hogue, Ramkumar, Dunlop, & Kramer, 2011). The present population-based cohort study tracks the younger siblings of children diagnosed with ASD in Israel to investigate the interpregnancy interval and related phenomena of birth-spacing and birth-order as risk factors for ASD recurrence as the primary objective. A secondary and related objective is to estimate "life-time" recurrence risk for ASD when children in the data are not observed into adulthood. In this context we investigate whether the cumulative risk of being diagnosed with recurrent ASD increases divergently with age as in Sandin et al. (2014).

2. Material and methods

2.1. Study design

The younger siblings of index cases (children diagnosed with ASD) in Israel are followed-up in a population-based cohort study to estimate recurrence risk for ASD as well as its risk factors. We use administrative data on the population of diagnosed cases of ASD in Israel for children born between 1992 and 2007 who were followed-up until June 2012, when the data were compiled. The database contains information on children diagnosed with ASD, their parents and their siblings in 9117 families. Data on dates of birth are used to calculate inter-pregnancy gaps between children with ASD and their immediate younger siblings, as well as birth gaps between younger siblings. Data on dates of ASD diagnosis in the general population and for cases of ASD recurrence are used to estimate the relationship between recurrence risk and age. Logit models are estimated to examine risk factors for ASD recurrence.

2.2. Study population

The study population consists of all children with ASD in the computerized records of the National Insurance Institute of Israel (NII). Since 1980 NII has provided benefits in cash and in kind to children with ASD. The benefit currently includes a monthly payment ($610 in 2013, equivalent to 25% of the average salary in Israel, and updated yearly) up to age 18, but it also makes parents eligible for other benefits and services. Since 1995 these benefits are not means-tested. If parents have two children with ASD they receive more than twice the benefit. Additional details about the NII database in relation to these benefits are available in Raz, Weisskopf, Davidovitch, Pinto, and Levine (2014).

Since NII benefits are substantial, the take-up rate is expected to be high if not comprehensive. Parents of children with ASD might not apply for benefit for reasons of privacy, or some children with ASD may go undiagnosed. The validity of ASD ascertainment in NII was assessed in a previous study (Raz et al., 2014), which found that NII records included 97% of cases from a major Israeli health maintenance organization.

Children with ASD in NII records were linked to their parents and siblings using their personal unique id numbers through data from the Population Registry of the Interior Ministry, which are available at NII. These records provide dates of birth of ASD children, their parents and their siblings, as well as data on ethnicity and kinship.

2.3. Diagnosis

In Israel ASD will typically be diagnosed by a multidisciplinary team, based on The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. The process of recognition at NII is described in detail elsewhere (Raz et al., 2014). In short, after the medical diagnosis parents may submit a claim to NII which will be handled by a professional committee. These committees will confirm or deny the claim, and in rare cases may also examine the child. Parents may appeal denial decisions.

The eligibility date for benefit will be the first date of symptoms, but not earlier than one year before the claim was submitted. Case status in this study was based on NII claim confirmations of child disability benefit for ASD.

2.4. Outcomes and covariates

The outcome under investigation is the recurrence of ASD among younger siblings of index cases. The covariates include the sex of index cases since there is evidence (Ritvo et al., 1989) that female index cases are more likely to have younger siblings with ASD, the sex of younger siblings since ASD is less prevalent among girls, the ages of mothers and fathers when younger siblings were born, and population groups (ultra-orthodox Jews, other Jews or Non-Jews who are mainly Arabs).

The data are used to construct various measures of birth-spacing and birth-order. To clarify our terminology, consider a family of four children in which the second child has ASD. The birth-order of the index case is therefore 2. The birth-order of his adjacent younger sibling is 3, and the birth-order of his non-adjacent sibling is 4. The "inter-pregnancy gap" (IPG) is defined as the difference between the dates of birth of sibling 3 and sibling 2. IPG refers specifically to birth gaps with respect to adjacent siblings of children with ASD. It is not defined for sibling 4 because sibling 4 is not adjacent to sibling 2. The "sibling gap" (sibgap) is defined as the difference between the dates of birth between adjacent siblings regardless of their ASD status. For example, sibgap for sibling 4 is the date of birth of sibling 4 minus the date of birth of sibling 3. Finally, the "birth gap" (bgap) is defined as difference between the dates of birth of younger siblings and index cases. For sibling 3 this