HHS Public Access

Author manuscript

J Autism Dev Disord. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

J Autism Dev Disord. 2015 July ; 45(7): 2056–2066. doi:10.1007/s10803-015-2368-y.

Inter-Pregnancy Intervals and the Risk of Autism Spectrum Disorder: Results of a Population-Based Study

Maureen S. Durkin, PhD, DrPH[1,2,3], **Lindsay Allerton, MPH**[1,2], and **Matthew J. Maenner, PhD**[2]

[1]Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, 789 WARF, 610 Walnut Street, Madison, Wisconsin, 53726, USA

[2]Waisman Center, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, Wisconsin, 53705, USA

[3]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison

Abstract

Recent studies have reported an increased risk of autism among second-born children conceived <12 versus >36 months after the birth of a sibling. Confirmation of this finding would point to inter-pregnancy interval (IPI) as a potentially modifiable risk factor for autism. This study evaluated the relationship between IPI and autism spectrum disorder (ASD) risk in a Wisconsin birth cohort of 31,467 second-born children, of whom 160 resided in the study area and were found to have ASD at age 8 years. In adjusted analyses, both short (<12) and long (>84 month) IPIs were associated with a two-fold risk of ASD relative to IPIs of 24-47 months ($p<0.05$). The long IPI association was partially confounded by history of previous pregnancy loss.

Keywords

autism; pregnancy intervals; epidemiology; risk factors

Introduction

Rises in the reported prevalence and awareness of autism spectrum disorder (ASD) in recent years (CDC 2008; Croen et al. 2002) have led to increased interest in identifying potentially modifiable risk factors for this neurodevelopmental disorder (Rice et al. 2013). One such risk factor, suggested in a large, California birth cohort study (Cheslack-Postava, et al. 2011)

Correspondence: Maureen S. Durkin, Department of Population Health Sciences and Pediatrics, University of Wisconsin-Madison, 789 WARF, 610 Walnut Street, Madison, WI 53726 U.S.A, Tel: (608) 263-7507 mdurkin@wisc.edu.

Conflicts of Interest:
The authors have no conflicts of interest to declare.

Ethical Review:
This work was approved by the University of Wisconsin Health Sciences Institutional Review Board and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All analyses were based on de-identified administrative records.

and recently replicated in a cohort study from Norway (Gunnes, et al. 2013), is pregnancy spacing or, more specifically, a short interval between the birth of one child and the conception of the next. The California study found more than a three-fold increase in risk of autism in second-born children conceived after interpregnancy intervals (IPIs) less than 12 months versus ≥36 months (Cheslack-Postava, et al. 2011). It also found evidence of an inverse, linear association between IPI and autism, with the risk of autism declining as IPI increased (Cheslack-Postava, et al. 2011). Similarly, the Norwegian study found a two-fold increased risk of autistic disorder associated with IPIs <12 versus ≥36 months among second-born children, but reported some evidence of a curvilinear association, with ASD risk increasing slightly for IPIs >60 months (Gunnes, et al. 2013). Both of these studies were restricted to full sibling pairs in which the first-born did not have ASD, and evaluated whether second-born children with ASD were more likely to have short IPIs than second-born children without ASD. More recently, a case control study from Finland reported evidence of modest increases in ASD risk associated with both short and long IPIs (Cheslack-Postava, et al 2014).

The aim of the present study was to evaluate the association between IPI and ASD risk based on ASD surveillance data from a population-based cohort of Wisconsin children. In contrast to previous studies of the association between IPI and ASD, the present study included the full spectrum of ASD cases in a defined population and did not exclude all multiple-births or families with more than one child with autism. Because of these differences, confirmation in this study of an association between short IPIs and ASD risk would add to the generalizability of the finding and strengthen the case for IPI as a potentially modifiable risk factor for ASD. It would also point to the need for further studies to understand the mechanisms underlying the association. Because both short and long IPIs are associated with a number of perinatal complications, such as low birth weight and preterm birth (Zhu, et al 1999; Conde-Agudelo, et al 2006), which are themselves risk factors for ASD (Rice, et al. 2013), this study also evaluated whether any associations between IPI and ASD risk were independent of documented perinatal complications

Methods

We implemented a population-based, case-cohort study in which all second-born live births to mothers residing in a 10-county area of Southeastern Wisconsin during the years 1994, 1998 and 2000 served as the birth cohort and comparison group. Approximately one half of the births in Wisconsin each year are to mothers residing within the study area. The study area is included in the Autism and Developmental Disabilities Monitoring (ADDM) Network.

ADDM Network Methodology and ASD Case Definition

ASD cases were identified using the two-phase ADDM Network methodology. In the first phase, we identified source records to review based on a child's year of birth, residency in the surveillance area at age eight years, and International Classification of Diseases, Ninth Revision (ICD-9) billing codes for select childhood disabilities or psychological conditions. For children meeting age and residency requirements, the source files were screened for

behavioral or diagnostic descriptions defined by ADDM Network to be "triggers" for abstraction. Examples of abstraction triggers include statements such as "does not initiate interactions with others," and "prefers to play alone or engage in solitary activities." A documented ASD diagnosis was also considered a trigger for abstraction. If abstraction triggers were found, evaluation information from birth through the current surveillance year was abstracted into a single composite record for each child.

In the second phase, trained clinician reviewers determined ASD case status based on a comprehensive review of the abstracted records and classified children as having ASD if they had documented behaviors consistent with the American Psychiatric Association's *Diagnostic and Statistical Manual-IV, Text Revision (DSM-IV-TR)* criteria for a pervasive developmental disorder (PDD), including autistic disorder, Asperger disorder or PDD-not otherwise specified (PDD-NOS) (American Psychiatric Association 2000). To meet criteria for a PDD among children not meeting criteria for autistic disorder, the surveillance protocol required documentation of at least one "ASD discriminator" in addition to the behaviors necessary to meet *DSM IV-TR* criteria for a PDD. Examples of ASD discriminators include being oblivious to others in social situations, and demonstrating atypical and persistent attention to sensory input. Further details regarding the ADDM Network protocol for ascertaining ASD have been reported previously (CDC 2007; CDC 2012).

In summary, for the purpose of this study children with ASD included members of the birth cohort (described below) who resided in the surveillance area at the age of eight years during study years 2002, 2006 or 2008 and who received one or more developmental assessment for potential behavioral or developmental delays or disorders, and were found to meet *DSM IV-TR* criteria for autistic disorder, Asperger disorder or PDD-NOS. Although the ASD case definition includes all those with autistic disorder, Asperger disorder or PDD-NOS, the surveillance protocol was able to distinguish only two broad categories of ASD: autistic disorder; and other ASD. The "other ASD" category includes those with documented behavioral impairments sufficient to meet *DSM IV-TR* criteria Asperger disorder or PDD-NOS. It is possible that some cases in the "other ASD" category did meet criteria for autistic disorder but lacked sufficient documentation of behaviors to confirm this.

Information on IPI

IPI was calculated based on birth certificate information by subtracting the clinical estimate of gestational age at birth (in months) from the interval in months between the present birth and the previous live birth to the mother. We used two approaches to categorize IPI: one followed that of Cheslack-Postava and colleagues (2011) and included four categories (<12; 12-23; 24-35; and ≥36 months), with ≥36 months serving as the reference category for computation of odds ratios (ORs); the other included six categories, including the five 12-month categories of <12, 12-23, 24-35, 36-47, 48-59, 60-71 and 72-83 and a category of ≥84 months (Table 1). Among the IPI categories defined in our second approach, we found the lowest risk of ASD to occur in the categories spanning 24-47 months and, for this reason, have used IPI of 24-47 months as the reference group when computing ORs under the second approach to categorizing IPI (Table 1).

Birth Cohort

Data for the birth cohort were obtained from de-identified birth and infant death certificate information provided by the Wisconsin Department of Health Services. From an overall cohort of 100,669 live births in the population under surveillance, 99,835 survived to one year and among these, 32,525 were second-born. For the primary analysis, the cohort was restricted to second-born births to maximize comparability with previous studies and to control for birth order effects. Excluded from this cohort of 32,525, for the purpose of this study, were 1,058 (3.25%) infants lacking IPI information. This included 562 second-born infants within multiple birth pregnancies that were the mothers' first pregnancies resulting in live births, and therefore did not have relevant IPIs. Birth data for the remaining 496 infants lacking IPI information were missing pregnancy interval (N=493) or gestational age (N=3). Among the 31,467 second-born infants with complete IPI information, 160 living in the surveillance area were identified as having ASD at age eight years and serve as the ASD case group for this study (Table 1). IPI information for ASD cases was compared to that for the remaining cohort members not found to have ASD.

Infants from the cohort who moved out of the surveillance area before age eight are included in the final birth cohort (because we have no way to identify and exclude them). Selected demographic and perinatal characteristics of the study cohort and ASD cases are shown in Table 1.

Previous Pregnancy Losses

For 9,408 (29.9%) of births in the cohort of second-born infants, the birth certificate indicated that the mother had at least one previous pregnancy loss. Information was unavailable on the timing of these losses, including whether they occurred before the mother's first or between her first and second live birth. Therefore, only when births to mothers with a history of pregnancy loss are excluded from analysis can the IPI variable used in this study be interpreted strictly as the interval between the present and previous *pregnancy*; for births to mothers with a history of pregnancy loss it refers more specifically to the interval between the present pregnancy and the previous *live birth* to the mother. To allow both interpretations, we present analyses both including and excluding births to mothers with a history of pregnancy loss.

Statistical Analysis

Potential for confounding effects of maternal and paternal age, maternal education, and other variables was assessed by examining associations between each potential confounder and both ASD (Table 1) and IPI (Table 2). We used chi square tests to evaluate the statistical significance of associations between covariates and IPI categories, and univariate logistic regression to evaluate the relationship between covariates and ASD. Variables found to be associated with a p-value <0.10 with both ASD and IPI were considered to be potential confounders and/or potential mediators in the causal pathway between IPI and ASD risk.

We performed four multivariable logistic regression analyses with ASD status as the dependent outcome and IPI group and potentially confounding or mediating factors as the independent variables. Though not associated with IPI and, therefore not a potential

confounder, sex of the baby was included in all regression models because it is strongly associated with ASD status and was included in the adjusted analyses of the two previous studies of the association between IPI and autism (Cheslack-Postava, et al. 2011; Gunnes, et al. 2013).

The first regression model was intended to replicate, to the extent possible with the data available for this study, the analysis presented by Cheslack-Postava et al (2011), which compared three IPI categories to the reference category of ≥36 months and is restricted to a sub-sample of 18,191 children from the birth cohort that includes only singleton births to women with no history of pregnancy loss and with complete paternal age information on the birth certificate.

We present three additional regression models (models #2, #3 and #4) using the IPI category of 24-47 months as the reference category and distinguishing five additional categories. Model #2 uses the full cohort of second-born births with complete IPI and other information (N= 31,440) and adjusts for factors considered likely confounders but not mediators of the association between IPI and ASD. These variables include maternal age and education, sex of the baby, and birth year. In addition, this model includes first trimester prenatal care, a potential marker of socioeconomic disadvantage and perinatal risk. Although paternal age and C-section were potential confounders, once maternal age and other co-variates were included in the models, they were not significantly associated with ASD and their inclusion in the models did not affect the ORs for IPI categories. For this reason, we excluded these variables from model #2.

Model #3 is similar to model #2 except that in developing it, we tested the effects of variables that are associated (at a significance level of $p<0.10$) with both IPI and ASD risk but that might function as intervening rather than confounding variables. These variables included low birth weight, preterm birth, small-for-gestational-age, gestational diabetes, and Caesarian delivery. We found the inclusion of these variables individually had little effect on the adjusted OR for the association between IPIs and ASD. Because of multicolinearity and lack of independence between some of these variables, we included only two of them, low birth weight and gestational diabetes, in model #3. Model #4 is similar to model #3 but restricted to births to mothers without a history of pregnancy loss (N= 22,034). Because of this restriction, the ORs for IPIs in model #4, as in model #1, can be interpreted strictly as the association between IPI and ASD, whereas in models #2 and #3, the IPI variable refers more specifically to the interval between conception of the index child and the mother's previous live birth.

Our general approach to missing data was to perform complete case analyses. For all variables included in the final models, this approach is justified by the rarity of missing data (<2% for IPI and <1% for any covariate). Although paternal age was missing for a relatively large percentage of the cohort (16.5%), only model #1 included paternal age as a covariate, and this model was restricted to those with complete paternal age information to enhance comparability with the findings of the Cheslack-Postava et al. (2011) study.

All analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina). This research was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board.

Results

The frequency distributions of IPI categories and available covariate information, by ASD status, are provided in Table 1. Also included in Table 1 are unadjusted odds ratios (ORs), 95% confidence intervals (CIs), and p-values for each variable, indicating association or lack of association with ASD. For the first categorization of IPI, with ≥36 months as the reference category, the unadjusted OR for IPI <12 months is 1.26 (95% CI 0.82, 1.95), and there are no statistically significant associations between IPI and ASD (Table 1).

In contrast, the unadjusted ORs for the finer categorization of IPI using the lowest ASD risk range of 24-47 months as the reference category show significant or nearly significant associations between both short and long IPIs and ASD risk (Table 1). These ORs suggest a U-shaped association between IPI and ASD, with the highest ASD risks associated with IPIs of <12 and ≥84 months. Other variables examined that were found to be significantly or nearly significantly ($p<0.1$) associated with ASD include maternal age, education and race, paternal age, sex of the child, birth year, birth weight, gestational age, history of gestational diabetes during the pregnancy, and first trimester prenatal care, Caesarian delivery and preterm birth (gestational age <37 weeks) (Table 1).

Among the variables shown in Table 1 to be associated with ASD, we found significant associations with IPI categories for all except sex of the baby (Table 2). Based on these analyses, we identified the following variables as potential confounding factors of ASD: maternal and paternal age<25, maternal education less than high school, and earlier birth year were negatively associated with ASD ($p<0.05$), while maternal age >35, white maternal race, and first trimester prenatal care were positively associated with ASD ($p<0.05$). Likewise, maternal and paternal age <25, maternal education less than high school, black maternal race were positively associated with short IPI ($p<0.05$), and first trimester prenatal care was negatively associated with short IPI ($p<0.05$). Long IPI was associated with parental age >35 and black maternal race. In addition, we identified the following variables as potential mediators of the IPI-ASD association: low birth weight; preterm birth; gestational diabetes during the pregnancy; and Caesarian delivery.

The results of the first multivariable regression analysis, which is our closest approximation to the model presented by Cheslack-Postava, et al. (2011), show that after adjustment for confounding factors, IPIs <12 months were associated with an 84% increased risk of ASD relative to IPIs ≥36 months (OR 1.84, 95% CI 1.03, 3.29) (Table 3).

The remaining three regression analyses, which use the IPI category of 24-47 months as the reference group, all showed a U-shaped association between IPI and ASD risk, with the highest risk of ASD in children with IPIs ≤12 months, followed by the category ≥84 months (Table 3). Model #2 uses the full sample of second-born children and adjusts for all potential confounders except for those that are potentially in the causal pathway between IPI and

ASD risk. This model shows that after adjustment for confounding factors, IPIs of ≤12 months is associated with more than a two-fold increased risk of ASD (OR 2.14, 95% CI 1.31, 3.50) (Table 3). IPIs ≥84 months were also associated with a two-fold increased risk of ASD (Table 3).

Adjustment for gestational diabetes and low birth weight had little effect on the ORs, indicating that the association between IPI and ASD risk cannot be explained by their respective associations with these pregnancy complications (Table 3, model #3).

The results of model #4, which includes the same covariates as model #3 but is restricted to births to mothers with no reported history of pregnancy loss, are similar to those of models #2 and #3, though the increased risk of ASD associated with IPIs ≥84 months was not significant (p=0.09) in this restricted sample (Table 3).

Table 4 provides the results included in model #2 stratified by whether the ASD cases was classified as “autistic disorder” versus “other ASD”. These results suggest that the U-shaped association between IPI and ASD risk may be restricted to cases classified as autistic disorder.

Discussion

We found that among second-born infants in this population-based cohort, those conceived between two and four years after a live birth had the lowest risk of ASD. Relative to this group and after controlling for confounding factors, infants with IPIs less than one year or ≥ seven years experienced approximately a two-fold increased risk of developing ASD. This U-shaped association between IPI and ASD was present in the cohort overall and among those meeting more restrictive inclusion criteria. These results are consistent with the two previous epidemiologic studies examining the association between IPI and autism risk in showing *short* IPI to be an independent risk factor (Cheslack-Postava, et al. 2011; Gunnes, et al. 2013). However, to our knowledge, this is the first study to show a comparably increased risk of ASD associated with *long* IPIs.

The causal mechanisms or explanatory factors underlying the associations with ASD most likely differ for short and long IPIs. Possible mechanisms affecting fetal neurodevelopment that have been suggested to explain the association between short IPIs and a range of adverse perinatal and developmental outcomes in offspring include maternal folate depletion (Gunnes, et al. 2013; Conde-Agudelo, et al. 2012; de Weger, et al. 2011; Smits and Essed 2001; van Eijsden, et al. 2008), incomplete resolution of the previous pregnancy and associated inflammation during the peri-conceptional period (Gunnes, et al. 2013; Conde-Agudelo, et al. 2012; Palm, et al. 2013), placental pathology (Conde-Agudelo, et al. 2012), and maternal stress during the closely-spaced pregnancy (Cheslack-Postava, et al. 2011; Gunnes, et al. 2013; Klerman, et al. 1998; Ronald, et al. 2011). The findings from this study call for further research with more detailed datasets to investigate these and other possible mechanisms underlying the association between short IPIs and ASD risk.

Possible explanations for the association between long IPIs and ASD risk include infertility and related complications and exposures (Conde-Agudelo, et al. 2006; Zhu, et al. 1999). Our

observation that the magnitude of the association between long IPI and ASD risk was only slightly attenuated after controlling for maternal age and pregnancy complications for which data were available, such as gestational diabetes and low birth weight, suggests that the association between long IPIs and ASD is largely not due to confounding by advanced maternal age and selected complications of pregnancy, which are themselves known risk factors for ASD (Schieve, et al. 2014; Croen, et al. 2007; Durkin, et al 2008; Grether, et al. 2009; Kolevzon, et al. 2007; Bilder, et al. 2009; Sandin, et al. 2012). The observations that long IPIs are associated with a history pregnancy loss (Table 2) and that the association between long IPIs and ASD was attenuated in the model restricted to births to mothers with no history of pregnancy loss (Table 3, model #4) points to a possible role of infertility in the association between long IPIs and ASD risk. These findings call for further replication of the association between long IPIs and ASD and, if replicated, further research to understand the mechanisms underlying this association.

Given the findings of this and previous studies of the association between IPI and ASD, future investigations of the etiology of ASD may benefit from stratification by IPI. For example, research into the association between maternal serum folate levels and ASD risk might benefit from studying samples enriched for pregnancies following short IPIs.

Applying Hill's (1963) criteria of consistency and strength of association, temporality, and biological plausibility for assessing the causality of associations between risk factors and health outcomes observed in observational studies, it is not unreasonable to suggest that the association between short pregnancy interval and ASD risk may be causal. With the publication of this study there are now three population-based studies showing ORs of two or greater for the association between short pregnancy interval and autism (Cheslack-Postava, et al. 2011; Gunnes, et al. 2013), and to our knowledge no studies showing a lack of association between short IPIs and ASD. The association between long IPI and ASD observed in this study is less consistent and perhaps less likely to be causal.

In addition to considering pregnancy complications as potentially confounding factors, it is possible that these complications are in the causal pathway between both short and long IPIs and ASD risk. Some pregnancy complications and other adverse perinatal or infant outcomes have been shown in previous research to have a U-shaped association with IPI that is similar to the one reported here for ASD (Conde-Agudelo, et al. 2006; Zhu, et al. 1999). Yet our finding, that adjustment for the pregnancy complications for which we had measures had little effect on the increased odds of ASD associated with both short and long IPIs, is consistent with previous research related to IPI and autism as well as cerebral palsy (Pinto-Martin, et al. 1998) in suggesting that the effect of IPI on adverse neurodevelopment is not entirely mediated by pregnancy complications.

Our finding of an increased risk of 'autistic disorder' associated with short IPIs, but no association between other ASD categories and short IPIs is somewhat consistent with the findings of Gunnes et al, which found an association between IPI and for autistic disorder but not other types of autism. Among the majority of our ASD cases classified as 'autistic disorder,' and we found a similar U-shaped association with IPI as we found for ASD overall. Among ASD cases not classified as 'autistic disorder', we found no association with

short IPIs but did find an adjusted OR of 2.72 (95% CI 0.99, 7.49) for IPIs ≥84 months. Two caveats to these findings should be noted. One is the relatively small number of ASD cases not in the 'autistic disorder' group (N=34), limiting the power to detect a significant association with IPI. The other is that the surveillance methodology allowed for only two sub-types of ASD cases: (1) those confirmed to meet DSM-IV-TR criteria for 'autistic disorder', and (2) all other ASD cases. It is possible that some of the ASD cases not confirmed to meet criteria for 'autistic disorder' did in fact meet these criteria but the surveillance system was able to find documentation only sufficient for the broader category of 'pervasive developmental disorder'. Further research is needed to clarify the associations between IPI ASD sub-types.

Important advantages of this study are that it is population-based and employed a validated and widely used approach to ASD casefinding (CDC 2007; CDC 2012; Bakian, et al. 2014). A limitation is the relatively small sample size, which limited our ability to evaluate consistency of the findings across sub-groups defined by gender, race/ethnicity, maternal education, or clinical characteristics such as co-occurring intellectual disability, or other variables. Another limitation of this study is its restriction to second-born children, which was done, as mentioned, to enhance comparability with previous studies and to control for birth order effects. In a separate analysis (data not shown), we included all second and later-born infants, adjusted for birth order, and found similar associations to those reported here for short IPIs but no significant association between long IPIs and ASD. Further studies with larger cohorts are needed to evaluate whether the association between IPIs and ASD risk varies by birth order.

A limitation of the case-cohort approach used in this study is that ASD case status could not be determined for an unknown number of cohort members who moved out of the surveillance area before age eight. For this reason, it was not possible to compute the cumulative incidence or prevalence of ASD in this cohort. It was possible, however, for the members of the cohort who were not identified as having ASD at age eight, including those who might have moved out of the surveillance area, to serve as a comparison group for the purpose of evaluating ASD risk factors. Despite efforts to control for confounding effects of variables for which we had measures, the results of our analyses could be biased due to unmeasured confounders or residual confounding.

Another limitation of this study is the absence of information on prenatal exposures, such as folic acid supplementation, that might reduce the risk of ASD associated with short IPI. Future birth cohort studies with prospective documentation of such exposures are needed to evaluate the potential for maternal folate levels to modify the effect of short IPI on ASD risk.

The association between short IPI and ASD has possible public health implications, as pregnancy spacing is a potentially modifiable risk factor. In the U.S., however, the proportion of births with short IPIs has increased in recent decades in association with the increased frequency of delayed childbearing and compression of the childbearing years (Nabukera, et al. 2009). At the same time, younger mothers disproportionately experience short IPIs and older mothers long IPIs (Table 2), a likely result of declining fertility with

age. Thus, from a population perspective, efforts to reduce the occurrence of short IPIs will have greater impact if they are able to reduce the frequency of short IPIs in younger mothers.

Conclusion

Further research with larger, population-based samples is needed to confirm the finding of a U-shaped association between IPI length and ASD risk, to better define optimal IPIs, and to inform public health objectives and recommendations (NCHS 2012; World Health Organization 2006). Research into the mechanisms underlying the association between IPI and ASD could lead to additional recommendations related to pregnancy readiness and family planning. It could also lead to important break-throughs in our understanding of the etiology and prevention of ASD.

Acknowledgments

This work was supported Centers for Disease Control and Prevention cooperative agreements UR3/CCU523235, UR3/DD000078, and UR3/DD000677. Additional support was provided by the University of Wisconsin-Madison Graduate School, and the National Institute of Child Health and Human Development grant P30HD03352.

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: American Psychiatric Association; 2000. text rev

Bakian AV, Bilder DA, Carbone PS, Hunt TD, Petersen B, Rice CE. Independent validation of autism spectrum disorder case status in the Utah Autism and Developmental Disabilities Monitoring (ADDM) Network site. Journal of Autism and Developmental Disabilities. 2014 published online 15 July 2014.

Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, Perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics. 2009; 123(5):1293–1300. [PubMed: 19403494]

Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, six sites, United States, 2000. MMWR. 2007; 56(SS-1):1–11.

Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites United States, 2008. MMWR. 2012; 61(3)

Cheslack-Postava K, Liu K, Bearman PS. Closely spaced pregnancies are associated with increased odds of autism in California sibling births. Pediatrics. 2011; 127:246–53. [PubMed: 21220394]

Cheslack-Postava K, Suominen A, Jokiranta E, Lehti V, McKaegue IW, Sourander A, Brown AS. Increased risk of autism spectrum disorders in short and long interpregnancy intervals in Finland. Joural of the American Academy of Child and Adolescent Psychiatry. 2014; 53(10):1074–81.

Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. JAMA. 2006; 295(15):1809–23. [PubMed: 16622143]

Conde-Agudelo A, Rosas-Bermudez A, Castano F, Norton MH. Effects of birth spacing on maternal, perinatal, infant, and child health: a systematic review of causal mechanisms. Studies in Family Planning. 2012; 43(2):93–114. [PubMed: 23175949]

Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. Journal of Autism and Developmental Disorders. 2002; 32(3):207–15. [PubMed: 12108622]

Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediat Adolesc Med. 2007; 161(4):334–40.

Durkin MS, Maenner MJ, Newschaffer CJ, Li LC, Cunniff C, et al. Advanced parental age and the risk of autism spectrum disorder. American Journal of Epidemiology. 2008; 168(11):1268–76. [PubMed: 18945690]

Grether JK, Anderson MC, Croen LA, Smith D, Windham GC. Risk of autism and increasing maternal and paternal age in a large North American population. American Journal of Epidemiology. 2009; 170(9):1118–26. [PubMed: 19783586]

de Weger FJ, Hukkelhoven CWPM, Serroyen J, te Velde ER, Smits LJM. Advanced maternal age, short pregnancy interval, and perinatal outcome. AJOG. 2011; 204:421.e1-9.

Downs JM, Jonas S. Short inter-pregnancy interval and schizophrenia: overestimating the risk. The British Journal of Psychiatry. 2012; 200(2):160. [PubMed: 22297590]

Gunnes N, Suren P, Bresnahan M, Hornig M, Lie KK, Lipkin WI, Magnus P, Nilsen RM, Reichborn-Kjennerud T, Schjolberg S, Susser ES, Oyen AS, Stoltenberg C. Interpregnancy interval and risk of autistic disorder. Epidemiology. 2013; 24(6):906–12. [PubMed: 24045716]

Hill, Austin Bradford. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine. 1965; 58(5):295–300. [PubMed: 14283879]

Klerman LV, Cliver SP, Goldenberg RL. The impact of short interpregnancy intervals on pregnancy outcomes in a low-income population. American Journal of Public Health. 1998; 88(8):1182–5. [PubMed: 9702144]

Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. Archives of Pediatric Adolesent Medicine. 2007; 161:326–33.

Nabukera SK, Wingate MS, Salihu HM, et al. Pregnancy spacing among women delaying initiation of childbearing. Arch Gynecol Obstet. 2009; 279:677–84. [PubMed: 18810476]

National Center for Health Statistics (NCHS). Healthy People 2020 Final Review. Hyattsville, Maryland: 2012. http://www.cdc.gov/nchs/data/hpdata2010/hp2010_final_review.pdf, http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicId=13

Palm M, Axelsson O, Wernroth L, Larsson A, Basu S. Involvement of inflammation in normal pregnancy. ACTA Obstetricia et Gynecologica. 2013; 92:601–5.

Pinto-Martin JA, Cnaan A, Zhao H. Short interpregnancy interval and the risk of disabling cerebral palsy in a low birth weight population. J Pediatr. 1998; 132:818–21. [PubMed: 9602192]

Rice CA, Rosanoff M, Dawson G, Durkin MS, Croen LA, Singer A, Yeargin-Allsopp M. Evaluating changes in the prevalence of autism spectrum disorders (ASDs). Public Health Reviews. 2013; 34(2):1–22.

Ronald A, Pennell CE, Whitehouse AJ. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front Psychol. 2011; 1:223. [PubMed: 21833278]

Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2012; 51(5):477–86. e1. [PubMed: 22525954]

Schieve LA, Tian LH, Baio J, Rankin K, Rosenberg D, Wiggins L, Maenner MJ, Yeargin-Allsopp M, Durkin M, Rice C, King L, Kirby RS, Wingate MS, Devine O. Population attributable fractions for three perinatal risk factors for autism spectrum disorders, 2002 and 2008 autism and developmental disabilities monitoring network. Ann Epidemiol. 2014; 24(4):260–66. [PubMed: 24529515]

Smits LJ, Essed GG. Short interpregnancy interval and unfaborable pregnancy outcome: role of folate depletion. Lancet. 2001; 358:2074–7. [PubMed: 11755634]

Smits L, Pedersen C, Mortensen P, Van Os J. Association between short birth intervals and schizophrenia in the offspring. Schizophrenia Research. 2004; 70:49–56. [PubMed: 15246463]

Todoroff K, Shaw GM. Prior spontaneous abortion, prior elective termination, interpregnancy interval, and risk of neural tube defects. Am J Epidemiol. 2000; 151(5):505–11. [PubMed: 10707919]

van Eijsden M, Smits LJ, van der Wal MF, Bonsel GJ. Association between short inter-pregnancy intervals and term birth weight: the role of folate depletion. Am J Clin Nutr. 2008; 88:147–53. [PubMed: 18614735]

World Health Organization. Report of a WHO Technical Consultation on Birth Spacing. Geneva: World Health Organization; 2006.

Zhu BP, Rolfs RT, Nangle BE, Horan JM. Effect of the interval between pregnancies on perinatal outcomes. The New England Journal of Medicine. 1999; 340(8):589–94. [PubMed: 10029642]

Abbreviations

ADDM	Autism and Developmental Disabilities Monitoring
ASD	autism spectrum disorder
CI	confidence interval
IPI	inter-pregnancy interval
OR	odds ratio
PDD-NOS	pervasive developmental disorder not otherwise specified

Table 1

Frequency of IPI Categories and Covariates Among Birth Cohort Members (Second-Born Infants in the Surveillance Area Who Survived Infancy, Birth Years 1994, 1998, 2000), Stratified by ASD Case Status at Age 8 Years, and Unadjusted ORs (95% CI) and p-values Indicating Associations with ASD.

Birth Characteristics	Control Group N (%) Total N=31,307	ASD Group N (%) Total N=160	Unadjusted OR (95% CI)	p-value
IPI (Cheslack-Postava[4] Categories)				
<12 months	4,870 (15.6)	32 (20.0)	1.26 (0.82, 1.95)	0.30
12-23 months	9,194 (29.4)	48 (30.0)	1.00 (0.68, 1.48)	0.99
24-35 months	6,490 (20.7)	24 (15.0)	0.71 (0.44, 1.15)	0.16
36+ months	10,753 (34.3)	56 (35.0)	1.00 (reference)	--
IPI (Six Categories)				
<12 months	4,870 (15.6)	32 (20.0)	1.94 (1.20, 3.15)	0.007
12-23 months	9,194 (29.4)	48 (30.0)	1.54 (0.99, 2.40)	0.053
24-47 months	10,054 (32.1)	34 (21.3)	1.00 (reference)	--
48-59 months	2,155 (6.9)	10 (6.3)	1.37 (0.68, 2.78)	0.38
60-83 months	2,358 (7.5)	15 (9.4)	1.88 (1.02, 3.46)	0.04
84+ months	2,676 (8.6)	21 (13.1)	2.32 (1.35, 4.01)	0.003
Mother's age				
<25 years	9,089 (29.0)	29 (18.1)	0.62 (0.40, 0.98)	0.04
25-29 years	8,821 (28.2)	46 (28.8)	1.00 (reference)	--
30-34 years	9,403 (30.0)	50 (31.3)	1.00 (0.67, 1.48)	0.99
35+ years	3,993 (12.8)	35 (21.9)	1.65 (1.07, 2.55)	0.02
Missing	1	0		
Mother's education				
Less than high school	4,464(14.3)	10 (6.3)	0.40 (0.20, 0.79)	0.008
High school graduate	9,509 (30.4)	53 (33.1)	1.00 (reference)	--
Some college	7,493 (24.0)	42 (26.3)	1.00 (0.68, 1.45)	0.98
College graduate	9,820 (31.3)	55 (34.4)	1.00 (0.67, 1.50)	0.99
Missing	21	0		
Mother's race				
White Non-Hispanic	23,017 (73.5)	130 (81.8)	1.00 (reference)	--
Black Non-Hispanic	4,893 (15.6)	19 (12.0)	0.69 (0.42, 1.11)	0.13
Other (includes Hispanic)	3,395 (10.8)	10 (6.3)	0.52 (0.27, 0.99)	0.05
Missing	2			
Father's age				
<25 years	3,257 (10.4)	7 (4.4)	0.37 (0.16, 0.82)	0.02
25-29 years	6,499 (20.8)	38 (23.8)	1.00 (reference)	--

Birth Characteristics	Control Group N (%) Total N=31,307	ASD Group N (%) Total N=160	Unadjusted OR (95% CI)	p-value
30-34 years	9,499 (30.3)	44 (27.5)	0.79 (0.51, 1.22)	0.29
35-40 years	4,883 (15.6)	34 (21.3)	1.19 (0.75, 1.89)	0.46
40+ years	1,993 (6.4)	17 (10.6)	1.46 (0.82, 2.59)	0.20
missing	5,176 (16.5)	20 (12.5)		
Sex of baby				
Male	15,935 (50.9)	119 (74.4)	2.80 (1.96, 4.00)	<0.0001
Female	15,372 (49.1)	41 (25.6)	1.00 (reference)	--
Birth year				
1994	10,399 (33.2)	35 (21.9)	0.56 (0.37, 0.84)	0.006
1998	10,289 (32.9)	61 (38.1)	0.98 (0.69, 1.40)	0.93
2000	10,619 (33.9)	64 (40.0)	1.00 (reference)	--
Gestational Diabetes				
No	30,376 (97.0)	149 (93.1)	1.00 (reference)	--
Yes	931 (3.0)	11 (6.9)	2.41 (1.30, 4.46)	0.005
1st trimester prenatal care				
No	4,097 (13.1)	10 (6.3)	1.00 (reference)	--
Yes	27,187 (86.9)	150 (93.8)	2.26 (1.19, 4.29)	0.01
Missing	23			
Gestational Age at Birth				
<37 weeks	2,021 (6.5)	15 (9.4)	1.50 (0.88, 2.56)	0.14
≥37 weeks	29,286 (93.5)	145 (90.6)	1.00 (reference)	--
Birth weight				
<1500 grams	167 (0.5)	4 (2.5)	4.81 (1.76, 13.12)	0.002
1500-2499 grams	1,268 (4.1)	7 (4.4)	1.11 (0.52, 2.37)	0.79
2500+ grams	29,871 (95.4)	149 (93.1)	1.00 (reference)	--
Missing	1			
Multiples				
No	30,851 (98.5)	158 (98.8)	1.00 (reference)	--
Yes	456 (1.5)	2 (1.3)	1.17 (0.29, 4.72)	0.83
History of pregnancy loss				
No	21,947 (70.1)	112 (70.0)	1.00 (reference)	--
Yes	9,360 (29.9)	48 (30.0)	1.01 (0.72, 1.41)	0.98
C-Section				
No	26,716 (85.3)	127 (79.4)	1.00 (reference)	--
Yes	4,591 (14.6)	33 (20.6)	1.51 (1.03, 2.22)	0.03

Table 2

Frequency of Selected Birth Characteristics of Birth Cohort Members (Second-Born Infants in the Surveillance Area Who Survived Infancy, Birth Years 1994, 1998, 2000), by IPI Categories, with p-Values Indicating Significance of Associations Between IPI Categories and Other Birth Characteristics.

	IPI Categories						
	<12 mo Total N=4,902 N (%)	**12-23 mo Total N=9,242 N (%)**	**24-47 mo. Total N=10,088 N (%)**	**48-59 mo Total N=2,165 N (%)**	**60-83 mo Total N=2,373 N (%)**	**≥84 mo Total N=2,697 N (%)**	**p-value**
Mother's age							<0.0001
<25 years	2265 (46.2)	2719 (29.4)	3027 (30.0)	589 (27.2)	449 (18.9)	69 (2.6)	
25-29 years	1221 (24.9)	2583 (28.0)	2661 (26.4)	663 (30.6)	968 (40.8)	771 (28.6)	
30-34 years	1038 (21.2)	2958 (32.0)	3200 (31.7)	591 (27.3)	608 (25.6)	1058 (39.2)	
35+ years	377 (7.7)	982 (10.6)	1200 (11.9)	322 (14.9)	348 (14.7)	799 (29.6)	
Missing	1	0	0	0			
Mother's education							<0.0001
<High school grad	1120 (22.9)	1239 (13.4)	1250 (12.4)	286 (13.2)	310 (13.1)	269 (10.0)	
High school grad	140 (29.2)	2347 (25.4)	3087 (30.6)	786 (36.4)	876 (37.0)	1036 (38.4)	
Some college	975 (19.9)	1960 (21.2)	2431 (24.1)	588 (27.2)	708 (29.9)	873 (32.4)	
College grad	1374 (28.1)	3695 (40.0)	3310 (32.8)	502 (23.2)	476 (20.1)	518 (19.2)	
Missing	3	1	10	3	3	1	
Mother's race							<0.0001
White	3296 (67.3)	7227 (78.2)	7721 (76.5)	1504 (69.5)	1564 (65.9)	1832 (67.9)	
Black	992 (20.2)	1129 (12.2)	1361 (13.5)	377 (17.4)	474 (20.0)	579 (21.5)	
Other	613 (12.5)	886 (9.6)	1005 (10.0)	283 (13.1)	335 (14.1)	286 (10.6)	
missing	1	0	1	1	0	0	
Father's age							<0.0001
<25 years	785 (16.0)	951 (10.3)	1070 (10.6)	188 (8.7)	201 (8.5)	69 (2.6)	
25-29 years	1059 (21.6)	2005 (21.7)	2067 (20.5)	437 (20.2)	530 (22.3)	439 (16.3)	
30-34 years	1188 (24.2)	3231 (35.0)	3240 (32.1)	599 (27.7)	593 (25.0)	692 (25.7)	
35-40 years	534 (10.9)	1334 (14.4)	1681 (16.7)	373 (17.2)	407 (17.2)	588 (21.8)	

	IPI Categories						
	<12 mo Total N=4,902 N (%)	**12-23 mo Total N=9,242 N (%)**	**24-47 mo. Total N=10,088 N (%)**	**48-59 mo Total N=2,165 N (%)**	**60-83 mo Total N=2,373 N (%)**	**≥84 mo Total N=2,697 N (%)**	**p-value**
40+ years	228 (4.7)	464 (5.0)	584 (5.8)	154 (7.1)	189 (8.0)	391 (14.5)	
missing	1108 (22.6)	1257 (24.2)	1446 (14.3)	414 (19.1)	453 (19.1)	518 (19.2)	
Sex of baby							0.3088
Male	2531 (51.6)	4731 (51.2)	5113 (50.7)	1098 (50.7)	1246 (52.5)	1335 (49.5)	
Female	2371 (48.4)	4511 (48.8)	4975 (49.3)	1067 (49.3)	1127 (47.5)	1362 (50.5)	
Birth year							<0.0001
1994	1746 (35.6)	3037 (32.9)	3373 (33.4)	679 (31.4)	675 (28.5)	924 (34.3)	
1998	1564 (31.9)	3089 (33.4)	3283 (32.5)	729 (33.7)	821 (32.0)	864 (32.0)	
2000	1592 (32.5)	3116 (33.7)	3432 (34.0)	757 (35.0)	877 (37.0)	909 (33.7)	
Gestational Diabetes							<0.0001
No	4799 (97.9)	9026 (97.7)	9800 (97.2)	2084 (96.3)	2272 (95.7)	2544 (94.3)	
Yes	103 (2.1)	216 (2.3)	288 (2.9)	81 (3.7)	101 (4.3)	153 (5.7)	
1st trimester prenatal care							<0.0001
No	1092 (22.3)	1074 (11.6)	1052 (10.4)	294 (13.6)	293 (12.4)	302 (11.2)	
Yes	3803 (77.7)	8163 (88.4)	9029 (89.6)	1871 (86.4)	2079 (87.7)	2392 (88.8)	
Missing	7	5	7	0	1	3	
Gestational Age							<0.0001
<37 weeks	383 (7.8)	522 (5.7)	590 (5.9)	140 (6.5)	161 (6.8)	240 (8.9)	
≥37 weeks	4519 (92.2)	8720 (94.4)	9498 (94.2)	2025 (93.5)	2212 (93.2)	2457 (91.1)	
Size for Gest. Age							<0.0001
Small for g.a.	209 (4.3)	331 (3.6)	387 (3.8)	116 (5.4)	144 (6.1)	179 (6.6)	
Appropriate for g.a.	4205 (85.8)	7805 (84.5)	8526 (84.5)	1827 (84.4)	1988 (83.8)	2246 (83.3)	
Large for g.a.	488 (10.0)	1106 (12.0)	1175 (11.7)	222 (10.3)	241 (10.2)	272 (10.1)	
Birth weight							<0.0001

	IPI Categories						
	<12 mo Total N=4,902 N (%)	**12-23 mo Total N=9,242 N (%)**	**24-47 mo. Total N=10,088 N (%)**	**48-59 mo Total N=2,165 N (%)**	**60-83 mo Total N=2,373 N (%)**	**≥84 mo Total N=2,697 N (%)**	**p-value**
<1500 grams	33 (0.7)	29 (0.3)	54 (0.5)	9 (0.4)	13 (0.6)	33 (1.2)	
1500-2499 grams	215 (4.4)	316 (3.4)	332 (3.3)	104 (4.8)	130 (5.5)	178 (6.6)	
2500+ grams	4654 (94.9)	8897 (96.3)	9702 (96.2)	2052 (94.8)	2230 (94.0)	2485 (92.2)	
missing	0	0	0	0	0	1	
Multiple Birth							0.0357
No	4845 (98.8)	9121 (98.7)	9927 (98.4)	2120 (97.9)	2341 (98.7)	2655 (98.4)	
Yes	57 (1.2)	121 (1.3)	161 (1.6)	45 (2.1)	32 (1.4)	42 (1.6)	
History of Pregnancy Loss							<0.0001
No	3819 (77.9)	6917 (74.8)	6904 (68.4)	1390 (64.2)	1441 (60.7)	1588 (58.9)	
Yes	1083 (22.1)	2325 (25.2)	3184 (31.6)	775 (35.8)	932 (39.3)	1109 (41.1)	
C-section							<0.0001
No	4313 (88.0)	7988 (86.4)	8646 (85.7)	1795 (82.9)	1956 (82.4)	2145 (79.5)	
Yes	589 (12.0)	1254 (13.6)	1442 (14.3)	370 (17.1)	417 (17.6)	552 (20.5)	

Table 3

Results of Multivariable Logistic Regression Analyses of Association Between IPI and ASD, Among Birth Cohort Members (Second-Born Infants in the Surveillance Area Who Survived Infancy, Birth Years 1994, 1998, 2000), with Adjusted ORs (95% CIs) and p-values.

	Adjusted OR (95% CI)	p-value
Model #1: *Best approximation of Cheslack-Postava[4] model, adjusted for maternal age, paternal age, maternal race, maternal education, and sex of baby, excluding those missing father's age, multiples, and those with history of pregnancy loss (N=18,191).*		
IPI Category		
<12 months	1.84 (1.03, 3.29)	0.04
12-23 months	1.11 (0.65, 1.91)	0.69
24-35 months	1.00 (0.55, 1.84)	0.99
36+ months	1.00 (reference)	--
Model #2: *using six IPI categories, adjusted for birth year, maternal education, maternal age, sex of baby, and 1st trimester prenatal care. Sample includes those missing father's age, multiples, and those with history of pregnancy loss (N=31,440)*		
IPI Category		
<12 months	2.14 (1.31, 3.50)	0.003
12-23 months	1.54 (0.99, 2.39)	0.06
24-47 months	1.00 (reference)	--
48-59 months	1.37 (0.67, 2.78)	0.39
60-83 months	1.80 (0.97, 3.32)	0.06
84+ months	2.09 (1.19, 3.67)	0.01
Model #3: *adjusted for birth weight and gestational diabetes, in addition to variables included in Model #2, inclusion criteria as in Model #2 (N=31,439)*		
IPI Category		
<12 months	2.16 (1.32, 3.53)	0.002
12-23 months	1.56 (1.00, 2.42)	0.05
24-47 months	1.00 (reference)	--
48-59 months	1.35 (0.67, 2.75)	0.40
60-83 months	1.77 (0.96, 3.28)	0.07
84+ months	1.98 (1.12, 3.48)	0.02
Model #4: *identical to Model #3 except that births to mothers with a history of pregnancy loss are excluded (N=22,034)*		
IPI Category		
<12 months	2.31 (1.33, 4.01)	0.003
12-23 months	1.32 (0.79, 2.23)	0.29
24-47 months	1.00 (reference)	--
48-59 months	1.18 (0.48, 2.89)	0.72
60-83 months	1.52 (0.68, 3.40)	0.31
84+ months	1.85 (0.91, 3.77)	0.09

Table 4

Results of Multivariable Logistic Regression Analyses Stratified by “Autistic Disorder” versus “Other ASD”, Showing the Association Between IPI and ASD Among Birth Cohort Members (Second-Born Infants in the Surveillance Area Who Survived Infancy, Birth Years 1994, 1998, 2000), with Adjusted ORs (95% CIs) and p-values.

	Adjusted OR (95% CI)	
IPI Category	**Autistic Disorder (n=120 cases)**	**Other ASD (n=34 cases)**
<12 months	2.75 (1.56, 4.84)	0.66 (0.18, 2.41)
12-23 months	1.80 (1.07, 3.03)	0.87 (0.34, 2.20)
24-47 months	1.00 (reference)	1.00 (reference)
48-59 months	1.81 (0.84, 3.93)	0.46 (0.06, 3.60)
60-83 months	1.76 (0.83, 3.73)	1.95 (0.66, 5.79)
84+ months	1.92 (0.83, 3.73)	2.72 (0.99, 7.49)

Adjusted for birth year, maternal education, maternal age, sex of baby, and 1st trimester prenatal care. Sample and co-variates are consistent with Model #2 of Table 3. (N=31,440)