Birth Spacing and Risk of Autism and Other Neurodevelopmental Disabilities: A Systematic Review

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abstract

CONTEXT: Both short and long interpregnancy intervals (IPIs) have recently been associated with increased risk of autism spectrum disorder (ASD). However, this association has not been systematically evaluated.

OBJECTIVE: To examine the relationship between birth spacing and the risk of ASD and other neurodevelopmental disabilities.

DATA SOURCES: Electronic databases from their inception to December 2015, bibliographies, and conference proceedings.

STUDY SELECTION: Observational studies with results adjusted for potential confounding factors that reported on the association between IPIs or birth intervals and neurodevelopmental disabilities.

DATA EXTRACTION: Two reviewers independently extracted data on study characteristics, IPIs/birth intervals, and outcome measures.

RESULTS: Seven studies (1 140 210 children) reported an association between short IPIs and increased risk of ASD, mainly the former subtype autistic disorder. Compared with children born to women with IPIs of ≥36 months, children born to women with IPIs of <12 months had a significantly increased risk of any ASD (pooled adjusted odds ratio [OR] 1.90, 95% confidence interval [CI] 1.16–3.09). This association was stronger for autistic disorder (pooled adjusted OR 2.62, 95% CI 1.53–4.50). Three of these studies also reported a significant association between long IPIs and increased risk of ASD. Short intervals were associated with a significantly increased risk of developmental delay (3 studies; 174 940 children) and cerebral palsy (2 studies; 19 419 children).

LIMITATIONS: Substantial heterogeneity, and few studies assessing neurodevelopmental disabilities other than ASD.

CONCLUSIONS: Short IPIs are associated with a significantly increased risk of ASD. Long IPIs also appear to increase the risk of ASD.

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REVIEW ARTICLE

Neurodevelopmental disabilities are a diverse group of chronic disorders that begin at any time during the development process (including conception, birth, and growth) up to 22 years of age and last throughout an individual's lifetime.[1] Major disabilities include intellectual disability, learning disabilities, communication disorders, autism spectrum disorder (ASD), and cerebral palsy, among others. In 2007, it was estimated that >200 million children <5 years of age in developing countries suffer from some kind of developmental delay or disability.[2] In the United States, neurodevelopmental disabilities affect 15% of children aged 3 to 17 years (nearly 10 million children in 2006–2008),[3] and ~1 in 68 children has been identified with ASD.[4]

Most neurodevelopmental disabilities are thought to be caused by a complex mix of factors, which vary depending on the particular disorder and the individual. These factors include genetics, environment, parental health and behaviors during pregnancy, complications during birth, and perinatal infections. Recent findings suggest an early prenatal origin of some neurodevelopmental disorders such as ASD.[5,6] In addition, several studies have found associations between prenatal and perinatal conditions and the risk of ASD,[7,8] attention-deficit/hyperactivity disorder,[9,10] developmental delay or disability,[11,12] and cerebral palsy.[13,14]

There is compelling evidence from several systematic reviews and meta-analyses that both short and long intervals between pregnancies are associated with an increased risk of adverse maternal, perinatal, infant, and child outcomes.[15–23] The relationship between birth spacing and the risk of neurodevelopmental disabilities has received less attention. In 2005, a World Health Organization technical consultation on birth spacing recommended conducting studies that investigate the impact of birth spacing on the psychological and neurologic development of children.[24] This topic is relevant to public health and clinical practice because if short and/or long intervals are independently associated with an increased risk of ASD and other neurodevelopmental disabilities, helping women and couples achieve healthy pregnancy spacing might contribute to reducing such adverse outcomes. Hence, we performed a systematic review whose primary aim was to compile and critically assess the existing evidence on the relationship between birth spacing and the risk of ASD and other neurodevelopmental disabilities through the use of formal methods for systematic reviews and meta-analytic techniques.

METHODS

This systematic review was conducted following a prospectively prepared protocol and reported in accordance with recommended methods for systematic reviews of observational studies.[25] Two of the authors (A.C.-A., A.R.-B.) independently retrieved and reviewed studies for eligibility, assessed their risk of bias, and extracted data. All disagreements encountered in the review process were resolved through consensus.

Study Selection

We included studies that met the following criteria:

1. Study design: cohort, cross-sectional, or case-control studies that evaluated the relationship between birth spacing and the risk of any neurodevelopmental disability in the younger child of a pair of siblings (index child).
2. Exposure: use of any interval preceding the birth of the younger sibling (interpregnancy interval [IPI], defined as the time elapsed between the birth of the immediate older sibling and the conception of the younger sibling; or birth interval, defined as the time elapsed between the birth of the immediate older sibling and the birth of the younger sibling) as the measure of birth spacing.
3. Outcome measures: the primary outcome measure of interest was ASD. The latest revision of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) merged all autism disorders into the umbrella term "autism spectrum disorder" without a definition of subtypes. However, we also assessed the association between birth spacing and the former autism subtypes "autistic disorder", "pervasive developmental disorder-not otherwise specified" (PDD-NOS), and "Asperger disorder." Secondary outcome measures included developmental delay, cerebral palsy, intellectual disabilities, communication disorders, attention-deficit/hyperactivity disorder, specific learning disorder, motor disorders, hearing loss, vision impairment, and other neurodevelopmental disabilities.
4. Statistical analysis: the authors of the studies must have adjusted the results for potential confounding factors. Studies were excluded from the review if they exclusively used univariate (unadjusted) analysis, if they used only the interval after the birth of the index child (succeeding interval), or if they did not provide data. Studies included in the systematic review were also included in the meta-analyses if they used IPI as the measure of birth spacing, provided data for ≥4 IPI strata, and reported unadjusted and/or adjusted odds ratio (OR) or relative risk (RR) estimates and 95% confidence intervals (CIs) or data to calculate them.

Data Sources and Searches

A literature search was undertaken in Medline, Embase, POPLINE, CINAHL, LILACS, and ECLA (all from inception to December 31, 2015) by using a combination of key words and text words related to "birth spacing" and "neurodevelopmental disabilities" (see Supplemental Table). Google Scholar, proceedings of congresses on pediatric neurology and neurodevelopmental disabilities, reference lists of identified studies, and review articles were also searched. No language restrictions were applied. If study findings were published in >1 source, we included only the most recent or complete study and supplemented if additional information appeared in other publications.

Assessment of Risk of Bias

Study quality was assessed by using 6 criteria deemed by the authors to be important for the quality of observational studies evaluating the association between birth spacing and neurodevelopmental disabilities. The assessments were judged as "low risk," "high risk," or "unclear risk" of bias. The criteria evaluated and how they were interpreted were as follows:

1. Measure of birth spacing used. "Low risk of bias": the study used IPI as measure of birth spacing; "high risk of bias": the study used birth interval as measure of birth spacing.
2. Categorization of exposure. "Low risk of bias": the study examined ≥4 categories of pregnancy intervals; "high risk of bias": the study examined <4 categories of pregnancy intervals.
3. Ascertainment of outcomes. "Low risk of bias": based on medical records or direct assessment or validated outcomes if administrative databases were used; "high risk of bias": based exclusively on a report that comes from patients or relatives or unvalidated outcomes if administrative databases were used.
4. Blinding. "Low risk of bias": assessment of both birth spacing status and outcomes was performed while investigators were blinded; "high risk of bias": assessment of birth spacing status or outcomes was not blinded.
5. Loss to follow-up or exclusions (only for cohort and cross-sectional studies) or period of time for recruitment of children (only for case-control studies). "Low risk of bias": loss to follow-up or nonvalid exclusions (improper elimination of records) were <10% (for cohort studies) or case patients and controls recruited during the same period of time (for case-control studies); "high risk of bias": loss to follow-up or nonvalid exclusions were ≥10% (for cohort studies) or children recruited from different periods of time (for case-control studies).
6. Control for confounding factors and assessment of mediating factors. "Low risk of bias": the study controlled for maternal age and at least 1 measure of socioeconomic status (eg, occupation and work status, educational level, income, or housing) and tested whether the association between birth spacing and ASD/other neurodevelopmental disabilities was mediated through preterm birth or low birth weight; "high risk of bias": the study did not control for maternal age and at least 1 measure of socioeconomic status or did not test the mediator effect of preterm birth or low birth weight.

If there was insufficient information available to make a judgment about these criteria, then they were scored as "unclear risk of bias."

Data Extraction

Data were extracted by using a specifically designed form for capturing information on study design, characteristics of the study population, sample size, measure of birth spacing used, categorization of intervals, measures of outcome, study quality, and unadjusted and adjusted ORs or RRs with their 95% CIs for individual neurodevelopmental disabilities associated with all pregnancy intervals. We contacted authors to obtain additional or missing data.

Data Synthesis and Statistical Analysis

Pooled unadjusted and adjusted ORs for the association between IPI and the risk of any ASD and the former subtype autistic disorder were calculated. Data available from studies allowed us to categorize IPIs into <12, 12 to 23, 24 to 35, and ≥36 months as well as <12, 12 to 23, 24 to 59, and ≥60 months. The referent categories used were ≥36 and 24 to 59 months, respectively. Data extracted from each study were arranged in 2 × 2 tables. ORs with their 95% CIs for ASD and autistic disorder were then calculated separately for the predefined categories of IPIs. Results from different reports were combined to produce pooled unadjusted ORs with 95% CIs according to the Mantel-Haenszel method. According to data availability, we also calculated pooled adjusted ORs within each category using the estimated adjusted effect and its estimated SE (often obtained indirectly from the CI) reported in each study. Heterogeneity of the results among studies was tested with the quantity I^2.[26] A substantial level of heterogeneity was defined as an $I^2 \geq 50\%$.[26] We pooled results from individual studies using DerSimonian and Laird random-effects models[27] because substantial heterogeneity was present in most meta-analyses. We planned to explore potential

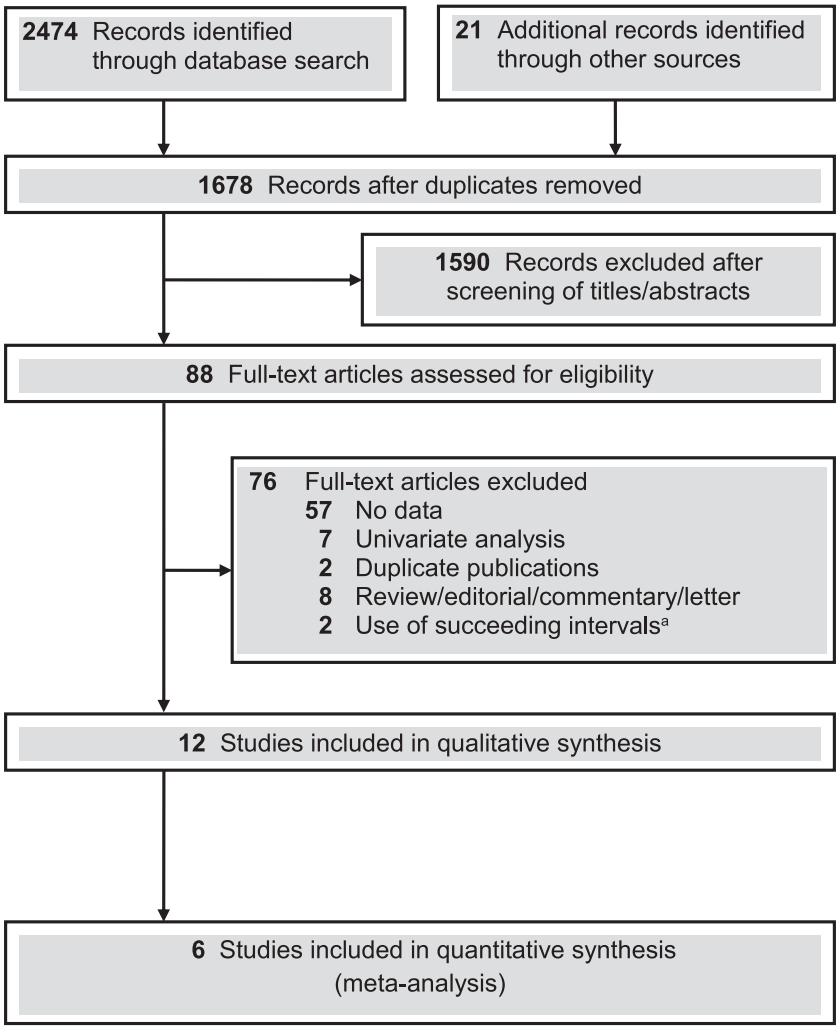

FIGURE 1
Study selection process. [a]Interval after the birth of the index child.

sources of heterogeneity, to perform subgroup and sensitivity analyses, and to assess publication and related biases if at least 10 studies were included in a meta-analysis. However, the limited number of studies allowed only the exploration of sources of heterogeneity according to study setting, sample size, and study quality.

For the relationship between birth spacing and other neurodevelopmental disabilities, we prepared a narrative synthesis on the basis of the overall results of the included studies because it was not possible to perform meta-analyses due to differences in measures of birth spacing, categories of intervals, reference categories, and outcome measures among the included studies.

All statistical analyses were performed by using Stata version 12.0 (StataCorp, College Station, TX) and Review Manager (RevMan) version 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark) statistical packages.

RESULTS

Selection, Characteristics, and Risk of Bias of Studies

Figure 1 summarizes the process of identification and selection of studies. The searches produced 1678 records, of which 88 were considered relevant. Of these, 76 were excluded, the main reason being lack of data on the relationship between birth spacing and neurodevelopmental disabilities considered. A total of 12 studies (6 cohort, 5 cross-sectional, and 1 case-control), including 1 334 569 children, met the inclusion criteria.[28–39]

The individual characteristics and main findings of the studies included in the systematic review are shown in Table 1. Seven studies provided data on ASD,[28–34] 3 on developmental delay,[35–37] and 2 on cerebral palsy.[38,39] Six studies were conducted in the United States, 2 each in Canada and Brazil, and 1 each in Norway and Finland. Ten studies used IPI and 2 used birth interval as measures of birth spacing. A "short interval" was defined in different ways, including IPIs of <3, <6, <12, <18, <24, and <36 months and birth intervals of <19 and <24 months. A "long interval" was defined as IPIs of ≥60, ≥72, and ≥84 months. Most of the studies that assessed the relationship between IPI and ASD adjusted their results for maternal and paternal age, child's gender, birth year, and at least 1 measure of socioeconomic status. Five studies[28,29,31,33,34] tested the effects of both preterm birth and low birth weight as potential mediators in the association between IPI and ASD risk. Among studies that evaluated the relationship between birth spacing and developmental delay and cerebral palsy, most of them included maternal age, measures of socioeconomic status, birth weight, gestational age, race/ethnicity, and child's gender as potential confounders/mediators in the adjusted models. The risk of bias for each included study is summarized in Fig 2. Seven studies met at least 5 of the criteria, 4 met 4 of the criteria, and 1 met 3 of the criteria. The most common deficiency was the inadequate categorization of pregnancy intervals.

TABLE 1 Characteristics of Studies Included in the Systematic Review

First Author, Year (Country)	Design (Sample Size)	Outcome	Interval Used; Interval Categories, mo	Confounding/Mediating Factors	Main Findings
Autism Spectrum Disorder					
Cheslack-Postava,[28] 2011 (United States)	Cross-sectional, population-based (662 730 children)	Autistic disorder (according to case files of the Department of Developmental Services; Asperger disorder and PDD-NOS were not included)	IPI; <12, 12–23, 24–35, 36–47, 48–59,[a] 60–71, 72–83, >84; and <12, 12–23, 24–35, ≥36[a]	Maternal and paternal age, race/ethnicity, maternal education, mother's birthplace, payment source for delivery, child's gender, birth year, preterm birth, low birth weight	Intervals <36 mo were associated with increased risk of autistic disorder (aOR 3.39, 95% CI 3.00–3.82 for intervals <12 mo; aOR 1.86, 95% CI 1.65–2.10 for intervals 12–23 mo; and aOR 1.26, 95% CI 1.10–1.45 for intervals 24–35 mo). No relationship between intervals ≥60 mo and autistic disorder.
Dodds,[29] 2011 (Canada)	Cohort population-based (129 733 children)	ASD (ICD-9 code 299 or ICD-10 code F84)	IPI; <18, ≥18[a]	Several maternal sociodemographic and obstetric factors; maternal conditions including psychiatric and neurologic disorders; income, factors related to labor/delivery; several perinatal factors including gestational age, birth weight, and infant gender; neonatal morbidities including anomalies, breastfeeding at discharge, sibling with autism, birth year	Intervals <18 mo were associated with increased risk of ASD (aRR 1.51, 95% CI 1.12–2.03).
Gunnes,[30] 2013 (Norway)	Cross-sectional, nation-based (223 476 children)	ASD (ICD-10 codes F84.0, F84.1, F84.5, F84.8, and F84.9), autistic disorder (ICD-10 code F84.0), and Asperger disorder (ICD-10 code F84.5) plus PDD-NOS (ICD-10 codes F84.1, F84.8, and F84.9) at age 8 y	IPI; <9, 9–11, 12–23, 24–35, ≥36[a]	Maternal and paternal age, maternal education, child's gender, birth year, preterm birth of the first-born child	Intervals <12 mo were associated with increased risk of autistic disorder (aOR 2.18, 95% CI 1.42–3.26 for intervals <9 mo; and aOR 1.71, 95% CI 1.07–2.64 for intervals 9–11 mo). Intervals of 9–11 mo were associated with increased risk of ASD (aOR 1.35, 95% CI 1.05–1.73). No relationship between intervals <24 mo and Asperger disorder and PDD-NOS.
Cheslack-Postava,[31] 2014 (Finland)	Nested case-control population-based (2208 children with diagnosis of ASD and 5163 controls)	ASD (ICD-10 codes F84.0, F84.5, F84.8, and F84.9), autistic disorder (ICD-10 code F84.0), Asperger disorder (ICD-10 code F84.5), and PDD-NOS (ICD-10 codes F84.8 and F84.9)	IPI; <12, 12–23, 24–59,[a] 60–119, and ≥120	Maternal and paternal age, parental psychiatric disorders, parity, previous miscarriage/abortions, any ASD diagnosis in a previous sibling, maternal socioeconomic status, previous miscarriage or abortion, date of birth, place of birth, infant gender, residence, preterm birth, low birth weight	Intervals <12 and ≥60 mo were associated with increased risk of ASD (aOR 1.50, 95% CI 1.28–1.74 for intervals <12 mo; aOR 1.28, 95% CI 1.08–1.52 for intervals 60–119 mo; and aOR 1.44, 95% CI 1.12–1.85 for intervals ≥120 mo). Only intervals <24 mo were associated with increased risk of autistic disorder (aOR 1.89, 95% CI 1.42–2.50 for intervals <12 mo; aOR 1.51, 95% CI 1.18–1.94 for intervals 12–23 mo). Only intervals <12 mo were associated with increased risk of PDD-NOS (aOR 1.55, 95% CI 1.22–1.97). Only intervals ≥60 mo were associated with increased risk of Asperger disorder (aOR 1.55, 95% CI 1.15–2.08 for intervals 60–119 mo; and aOR 1.71, 95% CI 1.13–2.60 for intervals ≥120 mo).

TABLE 1 Continued

First Author, Year (Country)	Design (Sample Size)	Outcome	Interval Used; Interval Categories, mo	Confounding/Mediating Factors	Main Findings
Coo,[32] 2015 (Canada)	Cohort population-based (41 050 children)	ASD (ICD-9 codes 299, 299.0, 299.8, and 299.9; ICD-10 codes F84.0, F84.1, F84.5, F84.8, and F84.9; or an ASD diagnosis in the Education or Children's Special Services databases)	IPI; <12, 12–23, 24–35, ≥36[a]	Child's gender, birth year, presence of an intellectual disability, maternal age at delivery, and whether the mother had ever received income assistance	There was no significant association between IPI and ASD (aOR 1.72, 95% CI 0.96–3.06 for intervals <12 mo; aOR 1.59, 95% CI 0.93–2.71 for intervals 12–23 mo; and aOR 1.29, 95% CI 0.70–2.38 for intervals 24–35 mo)
Durkin,[33] 2015 (United States)	Cohort population-based (31 467 children)	ASD (according to the American Psychiatric Association's DSM-IV-TR criteria for a pervasive developmental disorder, including autistic disorder, Asperger disorder, or PDD-NOS), autistic disorder, and Asperger disorder plus PDD-NOS at age 8 y	IPI; <12, 12–23, 24–47,[a] 48–59, 60–83, ≥84; and <12, 12–23, 24–35, ≥36[a]	Maternal and paternal age, maternal education, child's gender, birth year, first trimester prenatal care, history of pregnancy loss, low birth weight, preterm birth, small for gestational age, gestational diabetes, cesarean delivery	Intervals <12 and ≥84 mo were associated with increased risk of ASD (aOR 2.16, 95% CI 1.32–3.53 for intervals <12 mo; and aOR 1.98, 95% CI 1.12–3.48 for intervals ≥84 mo). Only intervals <24 mo were associated with increased risk of autistic disorder (aOR 2.75, 95% CI 1.56–4.84 for intervals <12 mo; and aOR 1.80, 95% CI 1.07–3.03 for intervals 12–23 mo). Intervals ≥84 mo were associated with marginally significant increased risk of Asperger disorder and PDD-NOS (aOR 2.72, 95% CI 0.99–7.49).
Zerbo,[34] 2015 (United States)	Cross-sectional (44 383 children)	ASD (ICD-9 codes 299.0, 299.8, and 299.9, and according to case files of the Department of Developmental Services)	IPI; <6, 6–8, 9–11, 12–23, 24–35, 36–47,[a] 48–59, 60–71, ≥72; and <12, 12–23, 24–35, ≥36[a]	Maternal and paternal age, child's gender, year of birth, maternal education, mother's race/ethnicity, place of birth, maternal BMI, change in BMI between pregnancies, maternal antidepressant use in the 3 mo before conception, ASD status of the first child, and birth weight, gestational age, and type of delivery of both first- and second-born child	Intervals <24 and ≥72 mo were associated with increased risk of ASD (aHR 3.0, 95% CI 1.9–4.7 for intervals <6 mo; aHR 2.1, 95% CI 1.4–3.3 for intervals 6–8 mo; aHR 1.9, 95% CI 1.3–2.8 for intervals 9–11 mo; aHR 1.5, 95% CI 1.1–2.1 for intervals 12–23 mo; and aHR 2.4, 95% CI 1.5–3.7 for intervals ≥72 mo).
Developmental delay					
Thompson,[35] 2003 (United States)	Cross-sectional (170 874 children)	Developmental delay or disability in the first 3 y of life (including delayed cognition, physical/motor impairment, lack of communication skills, delayed social/emotional development, or lagging adaptive development)	IPI; continuous	Maternal age, education, and marital and socioeconomic status; infant's gender, birth weight, antenatal care; race/ethnicity; smoking; complications of labor/delivery; congenital anomaly	Short intervals were associated with increased risk of developmental delay or disability in the first 3 y of life. The risk of developmental delay decreased significantly for each 1-mo increase in IPI since the birth of the previous sibling up to 60 mo (aOR for each 1-mo increase in IPI 0.995, 95% CI 0.993–0.997).
Pilz,[36] 2007 (Brazil)	Cross-sectional (197 children)	Suspected developmental delay up to age 6 y (using the Denver II test for social contact, fine motor skills, language, and gross motor skills)	BI; <19, ≥19[a]	Maternal age and education, familial income, marital status, parity, pregnancy complications, birth weight, gestational age, neonatal and child morbidity, child care, breastfeeding, maternal support	Intervals <19 mo were associated with increased risk of suspected developmental delay (aOR 3.90, 95% CI 1.02–24.08).

TABLE 1 Continued

First Author, Year (Country)	Design (Sample Size)	Outcome	Interval Used; Interval Categories, mo	Confounding/Mediating Factors	Main Findings
de Moura,[37] 2010 (Brazil)	Cohort (3869 children)	Suspected developmental delay at age 2 y (using the BSDI test for personal-social, adaptive, motor, communication and cognitive development)	BI; <24, ≥24[a]	Maternal age and education, race/ethnicity, antenatal care, child's gender, socioeconomic status, smoking, pregnancy complications, infant's mode of delivery, gestational age, birth weight, 5-min Apgar score, child nutritional variables, breastfeeding duration, mother and child morbidity, child environmental stimuli	Intervals <24 mo were associated with increased risk of suspected developmental delay (aRR 1.91, 95% CI 1.73–2.09).
Cerebral palsy					
Torfs,[38] 1990 (United States)	Cohort (19 044 children)	Cerebral palsy (diplegia, hemiplegia, quadriplegia, other spastic syndrome, athetosis, or cerebral palsy not otherwise specified that was not the result of a progressive disease or of a neural tube defect)	IPI; <3, 3–36,[a] >36	Race/ethnicity, parity, child's gender, mother's work, pregnancy complications, length of menstrual cycle, birth weight, gestational age, birth defects, delivery characteristics	Intervals <3 mo or >36 mo were associated with a marginally significant increased risk of cerebral palsy (aRR 3.7, 95% CI 1.0–4.4).
Pinto-Martin,[39] 1998 (United States)	Cohort (375 infants weighing 500–2000 g at birth)	Disabling cerebral palsy at a corrected age of 2 y (cerebral palsy plus any of the following conditions: inability to walk 5 steps unaided by age 2 y, receiving physical therapy for motor disability at the examination time, Bayley motor score >1 SD lower than performance score, surgical intervention for motor disorder, using braces or other physical assistance devices)	IPI; <6, ≥6[a]	Birth weight, gestational age, neonatal brain injury, maternal age, mother's education, amnionitis	Intervals <6 mo were associated with increased risk of disabling cerebral palsy (aOR 2.7, 95% CI 1.1–7.1).

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; ASD, autism spectrum disorder; BI, birth interval; BSDI, Battelle Screening Developmental Inventory; DSM-IV-TR, *Diagnostic and Statistical Manual, Fourth Edition, Text Revision*; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, 10th Revision; IPI, interpregnancy interval; PDD-NOS, pervasive developmental disorder-not otherwise specified.
[a] Reference category.

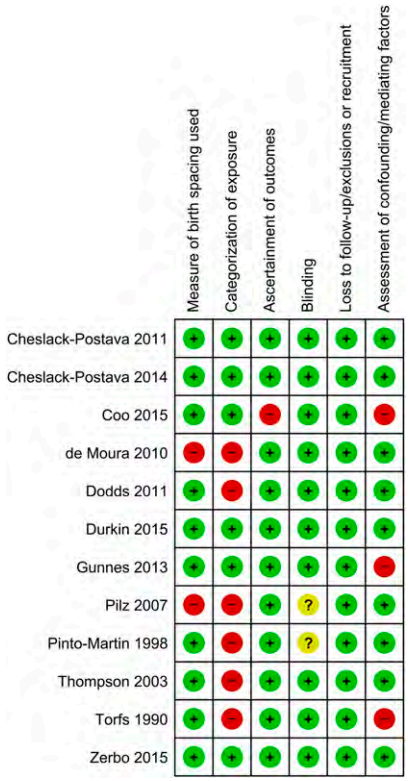

FIGURE 2
Risk of bias for each included study. Green symbols, low risk of bias; yellow symbols, unclear risk of bias; red symbols, high risk of bias.

Autism Spectrum Disorder

Seven studies conducted in developed countries, considered to be at low risk of bias and that included 1 140 210 children in total, assessed the relationship between IPI and ASD.[28–34] Three studies showed a U-shaped association between IPI and the risk of ASD.[31,33,34] Six studies found a significant association between short IPIs (<12 months,[30,31,33] <18 months,[29] <24 months,[34] and <36 months[28]) and increased risk of ASD. The remaining study reported a nonsignificant greater risk of ASD among children born after an IPI of <12 months (adjusted OR 1.72, 95% CI 0.96–3.06).[32] However, a sensitivity analysis restricted to individuals with more severe ASD revealed a significant association between IPIs of <12 months and this disorder. Three studies also found a significant association between ASD and long IPIs (≥60 months,[31] ≥72 months,[34] and ≥84 months[33]). Five studies reported a significantly increased risk of the former subtype autistic disorder associated with short IPIs.[28,30,31,33,34] No relationship was found between long IPIs and this disorder in 3 studies.[28,31,33] However, long IPIs were found to be associated with an increased risk of the former subtypes Asperger disorder and PDD-NOS in 3 studies.[31,33,34] Overall, there was no association between short IPIs and the risk of these 2 disorders.[30,31,33,34]

Table 2 shows the meta-analyses of the association between IPI and ASD. Children born to women with IPIs of <12 months had a significantly increased risk of ASD when compared with children born to women with intervals of ≥36 months (pooled adjusted OR 1.90, 95% CI 1.16–3.09). This association was stronger for the former subtype autistic disorder (pooled adjusted OR 2.62, 95% CI 1.53–4.50). There were no significant differences in the risk of ASD or autistic disorder between children conceived 12 to 35 months after a birth and those conceived ≥36 months after a birth.

TABLE 2 Meta-analyses of the Relationship Between IPI and ASD

IPI	No. of Studies[ref]	Children, *n*	Children With ASD, *n* (%)	Pooled Unadjusted OR (95% CI)	I^2, %	Pooled Adjusted OR (95% CI)	I^2, %
Any ASD							
<12 mo	5[28,30,32–34]	205 069	1533 (0.75)	1.58 (1.02–2.45)	94	1.90 (1.16–3.09)	96
12–23 mo	5[28,30,32–34]	343 509	1693 (0.49)	1.18 (0.84–1.66)	92	1.27 (0.89–1.83)	90
24–35 mo	5[28,30,32–34]	219 940	826 (0.38)	0.94 (0.73–1.19)	77	1.02 (0.80–1.29)	68
≥36 mo[a]	5[28,30,32–34]	233 634	899 (0.38)	1.00	NA	1.00	NA
Any ASD							
<12 mo	4[28,31,33,34]	169 825	1855 (1.09)	1.83 (1.33–2.54)	93	—[b]	—[b]
12–23 mo	4[28,31,33,34]	255 598	1913 (0.75)	1.32 (1.09–1.59)	80	—[b]	—[b]
24–59 mo[a]	4[28,31,33,34]	278 537	1619 (0.58)	1.00	NA	—[b]	—[b]
≥60	4[28,31,33,34]	41 991	665 (1.58)	1.37 (1.02–1.86)	83	—[b]	—[b]
Autistic disorder							
<12 mo	3[28,30,34]	190 546	1334 (0.70)	1.96 (1.29–2.97)	89	2.62 (1.53–4.50)[c]	88
12–23 mo	3[28,30,34]	318 888	1318 (0.41)	1.25 (0.84–1.85)	89	1.44 (0.84–2.47)[c]	91
24–35 mo	3[28,30,34]	205 397	602 (0.29)	1.03 (0.81–1.30)	61	1.14 (0.97–1.33)[c]	0
≥36 mo[a]	3[28,30,34]	215 588	563 (0.26)	1.00	NA	1.00	NA
Autistic disorder							
<12 mo	2[28,34]	163 383	1275 (0.78)	2.19 (1.66–2.88)	73	—[b]	—[b]
12–23 mo	2[28,34]	244 252	1229 (0.50)	1.51 (1.38–1.65)	0	—[b]	—[b]
24–59 mo[a]	2[28,34]	263 820	884 (0.34)	1.00	NA	—[b]	—[b]
≥60 mo	2[28,34]	35 488	126 (0.36)	1.15 (0.69–1.92)	82	—[b]	—[b]

NA, not applicable; ref, reference number.
[a] Reference category.
[b] It was not possible to estimate pooled adjusted ORs and I^2 tests because the reference categories did not coincide among the studies.
[c] Based on pooling of data from the studies by Cheslack-Postava et al[28] and Gunnes et al.[30]

When we categorized IPIs into <12, 12 to 23, 24 to 59, and ≥60 months, both short (<24 months) and long (≥60 months) IPIs were associated with a significantly increased risk of ASD (pooled unadjusted ORs [95% CIs]: 1.83 [1.33–2.54], 1.32 [1.09–1.59], and 1.37 [1.02–1.86] for IPIs of <12, 12–23, and ≥60 months, respectively) as compared with IPIs of 24 to 59 months. IPIs of <24 months were also associated with an increased risk of the former subtype autistic disorder (pooled unadjusted ORs [95% CIs]: 2.19 [1.66–2.88] and 1.51 [1.38–1.65] for IPIs of <12 and 12–23 months, respectively). It was not possible to estimate pooled adjusted ORs for these categories of IPIs because the reference categories did not coincide among the studies.

Substantial statistical heterogeneity among studies was present, as confirmed by I^2 values of ≥50% in most meta-analyses. A significant portion of the heterogeneity was explained by the study by Cheslack-Postava et al.[28] In fact, the exclusion of this study from the meta-analyses produced homogeneous pooled ORs (I^2 = 0% for most meta-analyses), which were not significantly different from the overall estimates obtained from all studies (all P > .40; data not shown).

Developmental Delay

Three studies, considered to be at moderate risk of bias, evaluated the relationship between birth spacing and developmental delay.[35–37] A large population-based study from the United States (N = 170 874)[35] found that short IPIs were associated with significantly increased risk of developmental delay or disability in the first 3 years of life. The risk of developmental delay decreased significantly for each 1-month increase in IPI since the birth of the previous sibling up to 60 months (OR for each 1-month increase in IPI 0.995, 95% CI 0.993–0.997). Two studies conducted in Brazil assessed the association between birth interval and suspected developmental delay at age 2 years[37] or up to age 6 years.[36] Both studies found that short birth intervals (<19 months[36] and <24 months[37]) were associated with a significantly higher risk of suspected developmental delay (adjusted OR 3.90, 95% CI 1.02–24.08[36]; adjusted RR 1.91, 95% CI 1.73–2.09[37]).

Cerebral Palsy

Two studies, rated as at moderate risk of bias, reported on the association between IPI and cerebral palsy.[38,39] One study in 19 044 children found that IPIs of <3 or >36 months were associated with a marginally significant increased risk of cerebral palsy (adjusted RR 3.7, 95% CI 1.0–4.4).[38] One small study (N = 375) reported that IPIs of <6 months were associated with a significantly increased risk of disabling cerebral palsy among infants who weighed 500 to 2000 g at birth (adjusted OR 2.7, 95% CI 1.1–7.1).[39]

DISCUSSION

Main Findings

The results of our systematic review show that, overall, short IPIs (<12 months and, possibly, 12 to 23 months) are independently associated with an increased risk of ASD, mainly the former subtype autistic disorder. This form is the most severe form of the conditions that comprise ASD because it is likely to co-occur with intellectual disability and a range of medical, behavioral, and psychiatric complications.[40] In addition, there was growing evidence that children born to women with long IPIs, possibly >5 years, are at increased risk of ASD, mainly the former subtypes Asperger disorder and PDD-NOS. There was emerging evidence that short intervals are associated with an increased risk of developmental delay. Less clear was the association between short intervals and cerebral palsy.

The reasons for the association between a short IPI and ASD are unknown. The fact that the birth spacing effects were not attenuated when child's gender, parental characteristics, and socioeconomic status were controlled for and that the IPI-ASD association was not mediated by preterm birth and low birth weight suggests that the effects are not caused by these confounding/mediating factors. A plausible explanation is the maternal folate depletion hypothesis, which claims that maternal serum and erythrocyte concentrations of folate decrease from midpregnancy onward and remain low during 4 to 12 months postpartum. Women who become pregnant before folate restoration is complete have an increased risk of folate insufficiency at the time of conception and during pregnancy.[16,41] As a consequence, there would be an early alteration in the fetal neurodevelopment that could lead to ASD in early childhood.[28] This hypothesis is reasonably supported by a recent, large population-based cohort study, which reported that periconceptional folic acid supplementation was associated with a significant reduction in the risk of autistic disorder in the offspring.[42] Interestingly, this study found that periconceptional supplementation of folic acid did not decrease the risk of Asperger disorder and PDD-NOS, which were not found to be associated with short IPIs in our review. Another study[30] found that the effect of short IPIs on the risk of autistic disorder appeared to be stronger in children whose mothers had not used folate before or during pregnancy, although this interaction was not statistically significant. Some cohort studies have reported that mothers who took periconceptional folic acid supplements had children with a reduced risk of neurodevelopmental disabilities,

such as severe language delay, behavioral problems, inattention, and hyperactivity and peer problems.[43–46] One relevant epigenetic process crucial to neurodevelopment is DNA methylation, which depends on the availability of dietary methyl donors such as folate, choline, and methionine. Insufficient folate intake can result in DNA hypomethylation, and hypomethylation is associated with potential neurodevelopmental consequences.[47]

Other mechanisms have been proposed to explain the increased risk of ASD associated with short intervals. Recent studies have shown that the majority of pregnancies after short intervals are unintended.[48–50] Moreover, unintended pregnancy is associated with a higher risk of prenatal maternal stress.[51,52] Gunnes et al[30] hypothesized that closely spaced pregnancies would be associated with increased maternal stress during the pregnancy of the index child, which increases the likelihood of developing ASD in this child. Indeed, there is some evidence that prenatal maternal stress is a risk factor for ASD.[53,54] In addition, a growing body of research suggests that early prenatal stress affects inhibitory neurons in the brain, which have been implicated in the pathophysiology of ASD.[55] An alternative mechanism could be through maternal inflammation because there is evidence of significant systemic inflammatory activity up to 9 to 10 weeks postpartum.[56] It has been proposed that when conception occurs at relatively short intervals after delivery, it is possible that persistent maternal inflammation may affect fetal neurodevelopment.[30,31] Finally, residual confounding may still be an explanation for this association.

Some hypotheses have also been proposed to explain the relationship between long intervals and ASD. It has been hypothesized that factors associated with long IPIs such as infertility,[33,34] unintended pregnancy,[31] and maternal inflammation[31] could explain the link between long IPIs and risk of ASD.

Strengths and Limitations

The strengths of our review are the rigorous methodology used, which adhered to the recommended guidelines for systematic reviews and meta-analysis of observational studies; the use of a prospective protocol designed to address a research question; the extensive literature searches without language restrictions; the exclusion of studies that did not adjust their effect estimates for potential confounding factors; the study quality assessment that was based on strict predetermined criteria; the inclusion of >1 million children in the studies that examined the association between IPI and ASD; and the quantitative and qualitative way of summarizing the evidence. Some limitations of this study should be acknowledged. First, there was an important degree of heterogeneity in most of the meta-analyses performed; therefore, pooled estimates should be interpreted cautiously. We explored the sources of heterogeneity and found that it was explained mainly by the largest study.[28] Nevertheless, the estimates of this study revealed the same direction of effect, which could suggest the absence of clinical heterogeneity among the studies. It is possible that the I^2 heterogeneity test could have excessive power when there are studies with a very large sample size, as was the case with the study by Cheslack-Postava et al.[28] Moreover, we used a random-effects model to pool results from individual studies, which provides the most useful and conservative estimate for informing practice in the presence of heterogeneity. Second, several included studies focused on the association between short intervals and the adverse outcomes considered, and little attention was given to the issue of long intervals. In addition, some studies did not properly address the potential confounding effects of some variables as well as the mediating effects of gestational age or weight at birth. Failure to make appropriate adjustment for potential confounding factors could lead to spurious associations or to inaccurate estimates of the strength of any real associations. Third, the number of studies available for analysis on the association between birth spacing and both developmental delay and cerebral palsy is still too small for us to draw conclusions. In addition, despite the broad scope of the literature search strategy, we were not able to find studies assessing the association between birth spacing and other neurodevelopmental disabilities. Finally, it was not possible to quantitatively combine data from the different studies that assessed the association between birth spacing and both developmental delay and cerebral palsy. However, it must be emphasized that meta-analysis is not the objective of a systematic review.[57]

Clinical and Public Health Implications

The finding that short IPIs are associated with an increased risk of ASD, and possibly of developmental delay, has important clinical and public health implications in both high- and low/middle-income countries because it is a potentially modifiable risk factor. For example, in the United States, there is evidence that the proportion of births after short intervals has increased as a consequence of the higher frequency of delayed childbearing and compression of the childbearing years.[48,58] In developing countries, approximately half of children are born after IPIs of <24 months.[59] Because advanced maternal age is also a well-recognized risk factor

for ASD,[60] educating women and their families about healthy timing and spacing of pregnancy (20–35 years of age[61] and 24–59 months,[62] respectively) could contribute significantly, in both developed and developing countries, to a reduction in this neurodevelopmental disorder. In addition, promotion of healthy timing and spacing of pregnancy substantially improves the perinatal, child, and maternal health.[62–64] The hypothetical impact of pregnancy spacing as an intervention to prevent ASD can be calculated by using the concept of population attributable-risk percentage, which expresses the proportion of ASD in the study population that is attributable to short IPIs and thus could be eliminated if such exposure was eliminated. By using pooled data from 5 studies shown in the top section of Table 2, we estimated that if families choose to delay a new pregnancy for at least 24 months after the preceding birth, the rate of any ASD among non-firstborn children would decrease by 23.0%; if families choose to delay the new pregnancy for at least 12 months, the rate of any ASD would decrease by 13.2%.

Implications for Research

Further studies will be needed to confirm the finding that long IPIs are also associated with increased risk of ASD, mainly the former subtypes Asperger disorder and PDD-NOS. Moreover, future studies should investigate the mechanisms underlying these associations and the possible modifier effect of periconceptional folic acid supplementation on the relationship between short IPIs and ASD. Finally, adequately powered studies that assess the relationship between birth spacing and other neurodevelopmental disabilities will also be required.

ABBREVIATIONS

ASD: autism spectrum disorder
CI: confidence interval
IPI: interpregnancy interval
OR: odds ratio
PDD-NOS: pervasive developmental disorder-not otherwise specified
RR: relative risk

Dr Conde-Agudelo conceived and designed the study, acquired and analyzed the data, performed statistical analysis, drafted the manuscript, and participated in the interpretation of findings; Ms Rosas-Bermudez and Dr Norton helped in conceiving and designing the study, acquired and analyzed the data, critically reviewed the manuscript, and participated in the interpretation of findings; and all authors approved the final manuscript as submitted.

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