Increased Risk of ADHD at Short and Long Interpregnancy Intervals in a National Birth Cohort

Running title: Interpregnancy Interval and ADHD

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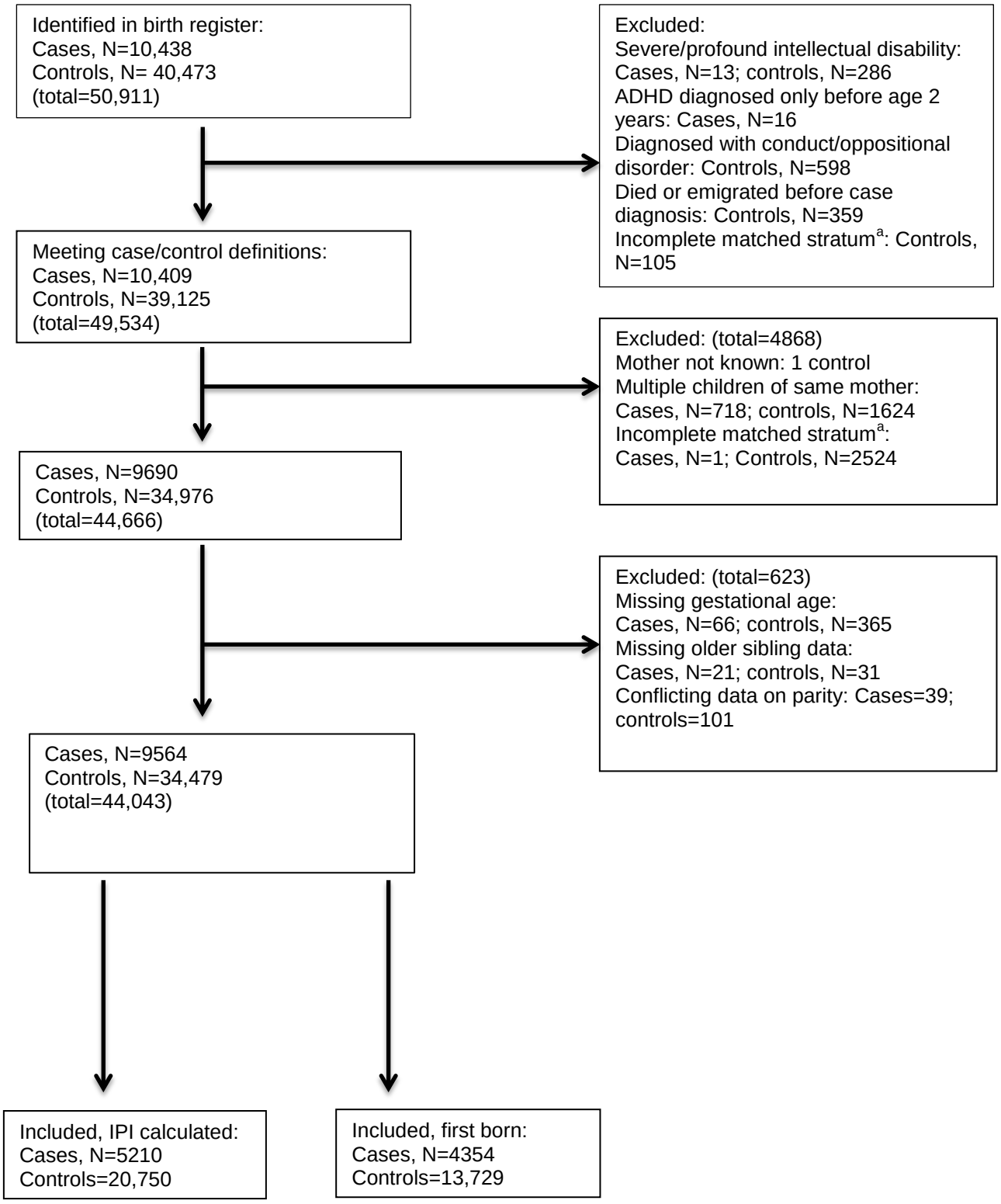
Supplemental Materials

eFigure 1. Selection of patients with ADHD and matched controls.
[a]Indicates subjects from a stratum that, following prior exclusions, no longer included at least one case and one control.



eTable 1. Median and mean interpregnancy interval (IPI) by levels of covariates, among non-firstborn controls.

	Controls (N=20,750)			IPI (months) among controls		
Covariate	**N**	**Median**	**Interquartile range**	**Mean**	**(SD)**	**p-value[a]**
Maternal age						<.001
≤19	82	10	5-19	13.5	11.6	
20-29	8431	19	12-31	24.7	19.5	
30-39	11399	31	17-59	44.0	38.0	
40+	838	57	24-130	81.8	69.5	
Paternal age[b]						<.001
<=19	22	16	6-37	23.0	22.4	
20-29	5629	18	11-30	25.7	24.7	
30-39	12440	27	15-49	38.2	34.1	
40+	2543	42	20-87	60.2	52.5	
Maternal parity						<.001
1	12054	22	13-39	33.4	34.0	
2	5819	35	18-64	46.9	40.1	
3 or more	2877	24	13-47	36.3	33.9	
Parental psychiatric diagnosis						<.001
Both parents	552	30	14-63	44.9	43.6	
Mother only	1915	27	14-54	40.5	38.4	
Father only	2026	25	14-50	39.4	39.0	
Neither parent	16257	25	14-46	36.8	35.3	
Mother's substance use history						<.001
No	20285	25	14-47	37.3	35.8	
Yes	465	33	15-72	51.4	49.3	
Maternal marital status[b]						<.001
Married/in relationship	19224	25	14-46	36.7	35.3	
Single	439	36	18-79	54.2	49.7	
Maternal immigrant status						0.01
Immigrated	294	25	13-64	42.7	41.4	
Did not immigrate	20456	25	14-47	37.5	36.2	
Maternal education						<.001
College/bachelor univ degree	4441	24	14-44	35.2	33.1	
Master/licenciate/PhD	1991	23	14-38	30.5	24.8	
None after elementary	3437	28	15-59	44.3	43.8	
Vocational/secondary grad	10881	25	14-48	37.8	36.3	
Paternal education[b]						<.001
College/bachelor univ degree	3252	24	14-42	34.4	31.9	
Master/licenciate/PhD	2177	23	14-40	32.8	28.9	
None after elementary	4080	27	14-54	42.0	41.5	
Vocational/secondary grad	11125	25	14-48	37.7	36.3	

[a] P-value for difference in mean IPI across levels of the covariate.

[b] Missing data for: paternal age and education (n=116), maternal marital status (n=1087).

eTable 2. Sensitivity analyses for the association between interpregnancy interval (IPI) and ADHD in Finnish births, 1991-2005.

	Model 1 [a,b] (N=39,955)		Model 2 [a,c] (N=43,401)		Model 3 [a,d] (N=16,096)		Model 4 [a,e] (N=25,483)		Model 5 [a,f] (N=42,329)	
IPI	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
<6 months	1.31	(1.12, 1.54)	1.30	(1.12, 1.51)	1.31	(1.10, 1.56)	1.24	(1.02, 1.51)	1.29	(1.10, 1.50)
6-11 months	1.00	(0.90, 1.11)	1.01	(0.91, 1.11)	1.01	(0.90, 1.14)	1.00	(0.88, 1.14)	1.02	(0.92, 1.13)
12-23 months	1.01	(0.92, 1.10)	1.00	(0.92, 1.09)	0.99	(0.90, 1.09)	0.97	(0.87, 1.08)	1.03	(0.94, 1.12)
24-59 months	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
60-119 months	1.15	(1.04, 1.43)	1.13	(1.02, 1.25)	1.11	(0.99, 1.24)	1.06	(0.93, 1.21)	1.09	(0.98, 1.20)
>=120 months	1.22	(1.04, 1.43)	1.25	(1.08, 1.45)	1.23	(1.04, 1.45)	1.31	(1.07, 1.61)	1.22	(1.05, 1.42)
First born, no IPI	1.33	(1.24, 1.43)	1.28	(1.19, 1.38)	excluded		1.34	(1.23, 1.47)	1.30	(1.22, 1.40)

[a] Models adjusted for: parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.
[b] Model 1, also adjusted for maternal marital status.
[c] Model 2, also adjusted for maternal parity.
[d] Model 3, excluding first born children.
[e] Model 4, excluding subjects with a maternal history of spontaneous or induced abortion.
[f] Model 5, also adjusted for maternal smoking during pregnancy; low birth weight and pre-term birth in the subject.

eTable 3. Odds ratios and 95% confidence intervals for the association between interpregnancy interval (IPI), using alternative categories, and ADHD in Finnish births, 1991–2005.

			Unadjusted (N=44,043)			Adjusted[a] (N=43,401)		
IPI	Cases N (%)	Controls N (%)	OR	95% CI		OR	95% CI	
IPI categorised as recommended by Hutcheon, et al.[b]								
<6 months	305 (3.2)	859 (2.5)	1.59	(1.36,	1.87)	1.27	(1.08,	1.51)
6-11 months	744 (7.8)	3131 (9.1)	1.05	(0.93,	1.18)	0.99	(0.87,	1.12)
12-17 months	722 (7.5)	3291 (9.5)	0.97	(0.86,	1.10)	0.97	(0.85,	1.10)
18-23 months	598 (6.3)	2656 (7.7)	1.00	(Reference)		1.00	(Reference)	
24-59 months	1646 (17.2)	7052 (20.5)	1.04	(0.93,	1.15)	0.98	(0.88,	1.10)
>=60 months	1195 (12.5)	3761 (10.9)	1.41	(1.26,	1.57)	1.13	(1.01,	1.27)
First-born, no IPI	4354 (45.5)	13,729 (39.8)	1.41	(1.28,	1.55)	1.32	(1.19,	1.46)
IPI categorised in 6 month intervals								
<6 months	305 (3.2)	859 (2.5)	1.74	(1.45,	2.08)	1.42	(1.18,	1.72)
6-11 months	744 (7.8)	3131 (9.1)	1.15	(0.99,	1.33)	1.11	(0.95,	1.29)
12-17 months	722 (7.5)	3291 (9.5)	1.06	(0.92,	1.23)	1.08	(0.93,	1.26)
18-23 months	598 (6.3)	2656 (7.7)	1.09	(0.94,	1.27)	1.12	(0.95,	1.31)
24-29 months	447 (4.7)	2117 (6.1)	1.02	(0.87,	1.20)	1.02	(0.86,	1.20)
30-35 months	314 (3.3)	1516 (4.4)	1.00	(Reference)		1.00	(Reference)	
36-41 months	279 (2.9)	1173 (3.4)	1.15	(0.96,	1.38)	1.08	(0.89,	1.30)
42-47 months	234 (2.4)	896 (2.6)	1.27	(1.05,	1.54)	1.18	(0.97,	1.45)
48-53 months	198 (2.1)	768 (2.2)	1.25	(1.02,	1.52)	1.16	(0.94,	1.43)
54-59 months	174 (1.8)	582 (1.7)	1.47	(1.20,	1.82)	1.44	(1.16,	1.80)
60-65 months	143 (1.5)	496 (1.4)	1.39	(1.11,	1.74)	1.14	(0.90,	1.44)
66-71 months	137 (1.4)	456 (1.3)	1.47	(1.17,	1.84)	1.25	(0.98,	1.59)
72-77 months	117 (1.2)	435 (1.3)	1.28	(1.00,	1.62)	1.12	(0.87,	1.44)
78-83 months	94 (1.0)	346 (1.0)	1.31	(1.01,	1.69)	1.11	(0.84,	1.47)
84-89 months	84 (0.9)	259 (0.8)	1.60	(1.21,	2.11)	1.34	(0.99,	1.79)
90-95 months	64 (0.7)	229 (0.7)	1.35	(0.99,	1.83)	1.05	(0.76,	1.45)
96-101 months	63 (0.7)	176 (0.5)	1.70	(1.24,	2.33)	1.46	(1.04,	2.04)
102-107 months	70 (0.7)	180 (0.5)	1.87	(1.38,	2.53)	1.52	(1.09,	2.11)
108-113 months	56 (0.6)	150 (0.4)	1.78	(1.28,	2.48)	1.47	(1.03,	2.09)
114-119 months	44 (0.5)	135 (0.4)	1.56	(1.09,	2.25)	1.30	(0.88,	1.91)
>=120 months	323 (3.4)	899 (2.6)	1.75	(1.47,	2.09)	1.37	(1.14,	1.65)
First born, no IPI	4354 (45.5)	13,729 (39.8)	1.54	(1.36,	1.75)	1.47	(1.29,	1.68)

[a] Adjusted for: parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.

[b] Hutcheon JA, Moskosky S, Ananth CV, et al. Good practices for the design, analysis, and interpretation of observational studies on birth spacing and perinatal health outcomes. *Paediatric and Perinatal Epidemiology* 2019;33:O15-O24.

Social media quote

Risk for ADHD diagnosis was increased among children born following interpregnancy intervals (IPI) <6 months or >60 months relative to those born following an IPI of 24-59 months in a national birth cohort-based study.

Synopsis

Study question

Is the interpregnancy interval (IPI) preceding a birth related to the risk of attention deficit hyperactivity disorder (ADHD) in the offspring?

What's already known

Short or long IPI may affect the conditions for fetal development and have consistently been associated with increased risk of autism spectrum disorders. Whether ADHD is also related to IPI has been largely unexplored.

What this study adds

Children born following interpregnancy intervals of <6 or ≥60 months were at increased risk for ADHD diagnosis relative to those born following an IPI of 24-59 months. Co-morbid autism spectrum disorders does not explain these associations.

Abstract

Background: Short or long interpregnancy interval (IPI) may adversely impact conditions for fetal development. Whether attention deficit hyperactivity disorder (ADHD) is related to IPI has been largely unexplored.

Objectives: To examine the association between IPI and ADHD in a large, population-based Finnish study.

Methods: All children born in Finland between 1991-2005 and diagnosed with ADHD (ICD-9 314x or ICD-10 F90.x) from 1995-2011 were identified using data from linked national registers. Each subject with ADHD was matched to 4 controls based on sex, date of birth, and place of birth. A total of 9564 subjects with ADHD and 34,479 matched controls were included in analyses. IPI was calculated as the time interval between sibling birth dates minus the gestational age of the second sibling. The association between IPI and ADHD was determined using conditional logistic regression and adjusted for potential confounders.

Results: Relative to births with an IPI of 24 to 59 months, those with the shortest IPI (<6 months) had an increased risk of ADHD (odds ratio [OR] 1.30, 95% confidence interval (CI) 1.12, 1.51) and the ORs for the longer IPI births (60-119 months and ≥120 months) were 1.12 (95% CI 1.02, 1.24) and 1.25 (95% CI 1.08, 1.45),, respectively. The association of longer IPI with ADHD was attenuated by adjustment for maternal age at the preceding birth, and co-morbid autism spectrum disorders did not explain the associations with ADHD.

Conclusions: The risk of ADHD is higher among children born following short or long IPIs although further studies are needed to explain this association.

Keywords: attention deficit hyperactivity disorder; autism spectrum disorder; interpregnancy interval; birth spacing; fetal development; pregnancy

Word count: 3390

Background

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate and impaired inattention, motor hyperactivity, and impulsivity.[1] ADHD is associated with deficits in academic, social, and occupational functioning, [2] is a risk factor for subsequent outcomes such as substance abuse [3] and injuries, [4] and results in substantial economic costs to society including those for health care, education, and lost productivity.[5]

While the high heritability [6] of ADHD and its association with genomic factors such as copy number variants [7] indicate an important role for genetics, the prenatal environment also appears to influence risk.[8] Prenatal factors that have been previously associated with increased risk for ADHD diagnosis or symptoms include earlier gestational age and impaired fetal growth,[9] lower maternal levels of thyroid hormone,[10] higher maternal levels of thyroid stimulating hormone,[11] and maternal smoking during pregnancy.[12]

Interpregnancy interval (IPI) is a potentially modifiable factor influencing the prenatal environment. Both short [13-18] and long [14,18] IPI have previously been associated with an increased risk for autism spectrum disorders (ASD), including within the Finnish population.[14] Although the specific mediators responsible for this association are not certain, the consistency of these associations provides strong evidence supporting a role for the prenatal environment in the developmental etiology of ASD.

According to two recent population-based register studies, 12% of patients with ADHD are also diagnosed with an ASD.[19,20] Siblings of persons with ASD have an increased risk of diagnosis with ADHD independent of their own ASD diagnosis,[21] and shared genetic risk loci for the disorders have been identified in genome-wide analyses.[22] The co-morbidity between the disorders, their shared genetic susceptibility, as well as overlap between risk factors such as male sex/gender and poor fetal growth [9,23] suggest that these conditions may share other risk factors. One previous study reported modestly increased risk of ADHD associated with IPI< 6 months with cousin-comparison and post-birth IPI analyses suggesting the presence of confounding by familial factors,[24] but to our knowledge this relationship has not been examined in other populations. Therefore, we investigated the association between IPI and diagnosis with ADHD using a large case-control study nested within a national birth cohort in Finland.

Methods

Data sources

Data used for the current study came from three linked national registries. The Finnish Hospital Discharge Register (FHDR) [25] includes all inpatient diagnoses since 1967 and outpatient diagnoses in specialized public hospital units since 1998. The Finnish Medical Birth Register (FMBR) includes information on the pre-, peri-, and neonatal periods up to age 7 days for all births in Finland since 1987. The Finnish Central Population Register (CPR) contains basic information about Finnish citizens and foreign permanent residents.

Case-control selection

The study used case-control data obtained for prior analyses.[9,19] Selection of ADHD cases and controls is illustrated in **eFigure 1**. Cases were born between 1991-2005 in Finland and had ADHD diagnoses (International Classification of Disease [ICD]-9: 314x and ICD-10: F90.x) occurring after the age of 2 years listed in the FHDR between 1995 and 2011, and no diagnoses of severe or profound intellectual disability, which would result in uncertain reliability of the ADHD diagnosis. Each case was individually matched with up to four controls, if available, on biological sex, date of birth (±30 days) and place of birth, as identified from the Finnish CPR. Controls were excluded if they died or emigrated from Finland before the case was diagnosed; or if they had a diagnosis of ADHD, profound/severe intellectual disability, or conduct/oppositional disorder, the last of which may have indicated misdiagnosed ADHD. This resulted in 10,409 subjects with ADHD and 39,125 controls initially identified from the birth register who met our criteria for case and control definitions.

We further excluded participants whose mother could not be identified (n=1), or who shared a mother with another participant (n=2342). Remaining members of matched sets were excluded if the case or all matched controls had previously been excluded (total n=2525). An additional 623 subjects were excluded because IPI could not be calculated due to missing data on gestational age or on the birth date of the preceding sibling; or due to conflicting information on maternal parity from different data sources. This resulted in a total of 9564 matched sets, each including one case with ADHD and up to 4 controls. Of these, 4354 matched sets had a first-born and 5210 matched sets had a case with defined IPI (see below).

Exposure

The exposure, IPI, was calculated using data from the FMBR and CPR. Sibships were identified for patients and matched controls, based on a shared biological mother, by linkage to the CPR. IPI was calculated in days as the difference between each participant's birth date and the birth date of their preceding sibling, minus the gestational age of the participant at birth. IPI in months was categorised into 6 levels (<6, 6-11, 12-23, 24-59 [reference], 60-119, and ≥120) for consistency with prior work in this cohort [14] and to capture intervals typically considered both short and long. First-born (no IPI) constituted a seventh category. Inclusion of the first-born category avoids the loss of subjects from strata where the case or all controls are first-born. Supplemental analyses categorised IPI by 6-month intervals to further examine the exposure-response relationship, and using categories recommended by Hutcheon *et al.* [26] to facilitate comparison across studies.

Covariates

Data on covariates were obtained from the FMBR and the FHDR. Covariates were selected as potential confounders based on previous evidence for an association with ADHD and/or IPI [9,14] and on their theoretical roles as shared common causes or proxies for common causes of ADHD and variation in IPI.[27] These included maternal and paternal age, education, and history of psychiatric diagnoses; and maternal parity, marital status, immigration status, and history of alcohol or substance use disorders. Parental psychiatric history and maternal alcohol/substance use disorders were defined as shown in Table 1. Maternal smoking during pregnancy, and infant low birthweight and preterm birth were examined as potential

explanatory factors for the IPI-ADHD association. Information on maternal history of spontaneous/induced abortion was obtained from the FMBR and comorbid ASD diagnosis in the subjects was determined based on ICD-10 (F84.0; F84.5; F84.8/F84.9) in the FHDR. All covariates pertained to the subject pregnancy, except for the psychiatric diagnoses, which included any lifetime diagnosis.

Statistical analysis

To assess the association between IPI and ADHD, conditional logistic regression models were fit. The first model was unadjusted. A second model adjusted for the following potential confounders: parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education. Additional models addressed the role of parental age. To address confounding by maternal age at the birth preceding the IPI,[26] a model was fit adjusted for this variable. First-born subjects were excluded because there is no preceding birth. To examine the association between IPI and ADHD not attributable to the parental ages at the subject birth, which may be clinically relevant to the assessment of offspring risk, maternal and paternal age at the subject birth were added to the initial adjusted model.

Effect modification of the associations between IPI and ADHD by comorbid diagnosis of ASD in the case was examined on the multiplicative scale by including terms for comorbid ASD and for comorbid ASD by IPI interactions in an adjusted model. All analyses were conducted using SAS statistical software (SAS Version 9.4; SAS Institute Inc., Cary, NC).

Sensitivity analysis

A series of sensitivity analyses were performed as follows: (i) Maternal marital status was added to a model including the subset of observations for which this information was available, in order to additionally test for potential confounding; (ii) A model was fit excluding subjects who were first-born, to assess the impact of including this group; (iii) To test for confounding by maternal parity, a model was fit including this variable; (iv) Because the IPI is measured between two live-birth pregnancies, women experiencing a miscarriage or abortion during this interval will have spent some of the time pregnant and may have different exposures or physiologic parameters than women who are non-pregnant during the interval. To address the possibility that this influenced our results, we fit a model restricted to the observations with no prior reported miscarriage or abortion; and (v) To test whether the association between IPI and ADHD was attributable to low birthweight, preterm birth, or maternal smoking during pregnancy, dichotomous terms for these variables were added to the model.

Missing data

Missing data for the potential confounders were addressed with complete case analysis; data were missing on one or more of these variables for 1.5% of observations.

Ethics approval

The study received approval from the Ministry of Social Affairs and Health of Finland and from the Institutional Review Board of the New York State Psychiatric Institute.

Results

Characteristics of the cases and controls are shown in **Table 1**. Subjects were 84.1% male. Cases with ADHD were more likely to have younger mothers and fathers; to be first-born; to have a history of parental psychiatric diagnoses in one or both parents; to have mothers with a history of substance use, who were single, or had immigrated to Finland; to have lower levels of parental education; and to be born low birthweight or preterm.

Among all non-firstborn controls, the median (interquartile range) IPI was 25 (14-47) months. IPI was positively correlated with the ages of both parents, but inversely related to the level of parental education. Maternal smoking, history of substance use, single marital status, and having immigrated to Finland were each associated with longer mean IPI. Median IPI was longer for third-born (maternal parity 2) controls than for those born second or fourth and later in the sibship. Among strata defined by parental history of psychiatric diagnosis, both parents having a diagnosis was associated with the longest median IPI (**eTable 1**).

Table 2 shows odds ratios (OR) for the association between IPI and ADHD. Relative to births with an IPI of 24–59 months, those with the shortest IPI (<6 months) had an increased risk of ADHD (OR 1.30, 95% confidence interval [CI] 1.12, 1.51) in covariate-adjusted models, while the adjusted ORs for longer IPI births (60–119 months and ≥120 months) were 1.12 (95% CI 1.02, 1.24) and 1.25 (95% CI 1.08, 1.45), respectively. First-born subjects also had increased odds of ADHD diagnosis relative to those born following an IPI of 24-59 months (adjusted OR 1.34, (95%

CI 1.25, 1.44). When IPI was categorized in 6-month intervals throughout the full range of values, the lowest risk of ADHD was seen among those with IPI 30-35 months and dose-response patterns were evident with both decreasing and increasing IPI (**Figure 1**). Results from the models applying additional adjustments or restrictions and those using alternative categories for IPI were consistent with those presented in **Table 2** and **eTables 2 and 3**).

Table 3 shows ORs for the association between IPI and ADHD adjusted for parental ages. When the model is adjusted for the maternal age at the birth preceding the IPI, the association with short IPI (<6 months) was strengthened (OR 1.34, 95% CI 1.12, 1.60) while that with long IPI (>=120 months) was attenuated (OR 1.15, 95% CI 0.97, 1.36). Adjustment for maternal and paternal ages at the subject birth, conversely, moderately reduced the magnitude of association for IPI<6 months (OR 1.25, 95% CI 1.07, 1.45) and strengthened that for IPI>=120 months (OR 1.37, 95% CI 1.18, 16.0).

Table 4 provides estimates for the association between IPI and ADHD by the presence or absence of a co-morbid ASD diagnosis in the case. Twelve percent of cases with ADHD (1171 of 9690) also had a comorbid diagnosis of ASD. The odds of ADHD with ASD were decreased among subjects with IPI <6 months (OR 0.34, 95% CI 0.14, 0.83) and not associated with other IPI categories.. Similar to the overall results, the odds of ADHD without ASD were increased for IPIs <6 months (OR 1.32, 95% CI 1.13, 1.55) and ≥120 months (OR 1.18, 95% CI 1.00, 1.38). Tests of heterogeneity indicated that the association between IPI <6 months and ADHD differed for cases with versus without ASD ($p_{interaction}$=0.003).

Comment

Principal findings

This population-based study, drawn from all births in Finland between 1991-2005, provides evidence that IPI of <6 or ≥60 months is associated with an increased risk of ADHD among second- and later-born children. The highest risk of ADHD was found among children born following IPI <6 months, and the association with IPI>=120 months was attenuated by adjustment for maternal age at the preceding birth. This association was not accounted for by co-morbid diagnosis with ASD, a condition that has previously been associated with short and long IPI. First-born children were also at increased risk of ADHD relative to those born following an IPI of 24-59 months.

Strengths of the study

A strength of this study was the use of national registry data with a large sample size and an unselected population. While this method does not allow for individual diagnostic confirmation, a validation study showed that 88% of subjects with a registry-based ADHD diagnosis met DSM-IV criteria for ADHD based on a parental interview.[20] Another important strength of the study was the use of registry data linked by personal identification numbers to accurately match siblings. This should have resulted in low misclassification with respect to IPI. Misclassification of IPI may occur due to incorrect estimation of gestational age; this would particularly impact shorter IPI pregnancies, where the relative impact on the estimation of IPI would be greater.

However, this is expected to be non-differential with respect to the outcome and would have biased estimates of association for shorter IPI pregnancies toward the null.

Limitations of the data

Our study relied on the FHDR to identify ADHD cases. While the diagnosis of ADHD in Finland is typically based on assessment by a specialist in psychiatry or neurology in public outpatient services, we likely missed less severe cases who did not utilize specialized services. The cumulative incidence of ADHD identified through the FHDR by age 21 for children born 1991-1993 was 2.3%, [19] somewhat lower than the estimated prevalence of 3.4% based on recent meta-analyses. [8] Therefore, our findings may not be representative of less severe cases of ADHD.

As with any observational study, we cannot rule out the possibility of bias due to unmeasured confounding. For example, we did not have the data on history of stillbirth or paternal age at the prior pregnancy as confounders. Based on the E-value,[28] an unmeasured confounder would have to be associated with both IPI and ADHD with a risk ratio of at least 1.92 each to fully explain the observed OR of 1.30 for the association of IPI <6 months with ADHD; or would have to be associated with IPI and ADHD by a risk ratio of at least 1.81 each to explain away the observed OR of 1.25 for the association of IPI ≥120 months with ADHD. For the lower limits of the confidence intervals, the corresponding values for the unmeasured confounders are 1.49 or 1.37, respectively. We could not compare multiple IPIs within the same woman. Finally, we

were unable to examine subsets of ADHD or clinical characteristics for potential heterogeneity in the relationship with IPI. This may be a fruitful area for future research.

Interpretation

The mechanisms explaining the observed associations may differ for short versus long IPI. Short IPI has been linked to nutritional depletion including lower levels of maternal folate (reviewed by Conde-Agudelo et al.[29]), and reduced levels of polyunsaturated fatty acids.[30] Maternal intake of these nutrients has also been linked to symptoms of ADHD. Lower maternal red blood cell folate in early pregnancy has been associated with higher levels of child hyperactivity,[31] while maternal consumption of oily fish (the major dietary source of omega-3 fatty acids) during early pregnancy was related to a reduced risk of hyperactivity among 9-year-old children.[32] Decreased IPI has also been linked to immunologic alterations, including increased recurrence of group B streptococci colonization,[33] altered cervical cytokine concentrations,[34] and unresolved inflammation from the prior pregnancy.[35] Supporting a potential immune-related etiology, maternal genitourinary infection has been associated with increased risk of ADHD diagnosis in a number of studies.[36-38] Recent systematic reviews focused on high-resource settings suggest increased risks of pre-term birth and small for gestational age following short IPI,[39] as well as obstetric complications such as gestational diabetes.[40] Though earlier gestational age and impaired fetal growth were previously associated with ADHD,[9] adjustment for low birthweight and preterm birth did not appreciably alter our results.

On the other hand, long IPI may be related to underlying infertility or associated with fertility treatment. Increased risks of ADHD have been reported in the offspring of women with fertility problems [41] and those using ovulation induction.[42] Adjustment for maternal age at the preceding birth in the subjects with this information available resulted in the attenuation of the OR and a 95% CI including 1.0, suggesting that maternal age at the preceding birth is a common cause or proxy for a common cause of long IPI and ADHD. An association of younger maternal age at first birth with an increased risk for offspring ADHD was previously found to be primarily due to genetic confounding [43]; here maternal age at the preceding birth may similarly be a marker for genetic risk for ADHD.

Both short and long IPI have been associated with a higher prevalence of unintended (unwanted or mistimed) pregnancy.[44] Women with an unintended pregnancy are more likely to smoke, to use alcohol or illicit drugs, to delay prenatal care, and are less likely to take prenatal vitamin supplements [45,46] than are women with intended pregnancies. Multivitamin use during early pregnancy has been associated with a decreased risk of ADHD diagnosis and treatment [47] while prenatal maternal alcohol [48] and illicit drug use [49] have been associated with increased levels of ADHD related behavior. Maternal smoking during pregnancy is also associated with offspring ADHD, however this may be largely explained through confounding by family-level factors.[50,51] In the current study, adjustment for maternal smoking during pregnancy had little impact on the results, suggesting that it did not explain the observed association.

Associations of ASD with both short and long IPI have previously been observed in this population.[14] Nonetheless, it is unlikely that ASD accounts for the relationship that we observed between IPI and ADHD given that the relationship between ADHD without comorbid ASD diagnosis was similar to that for an ADHD diagnosis overall. This suggests that the neurodevelopmental implications of IPI are not specific to autism and may potentially be broad, though this remains to be examined. Short IPI has previously been linked to increased risk of schizophrenia.[52-55] Closely spaced births have been associated with poorer performance on math and reading achievement tests;[56] lower verbal intelligence test scores;[57] and poorer performance on academic skills tests.[58] However, these studies are substantially limited by small sample sizes, selected populations, and limited adjustment for confounding. Therefore, further elucidating the specific developmental domains that may be impacted by IPI remains an important research goal.

The protective association between short IPI and ADHD with ASD should be interpreted with caution given the smaller sample size of this stratum and the exclusion of subjects with severe/profound intellectual disability, a co-morbidity often present with ASD. Thus, our cases with ADHD and ASD are unlikely to be directly comparable to ASD cases identified in other studies. Nonetheless, this underscores the importance of considering heterogeneity within both of these disorders. In fact, when ASD was examined previously by sub-types, IPI <12 months was associated with increased risk of childhood autism and of pervasive developmental disorder-not otherwise specified (PDD-NOS), but not of Asperger syndrome [14].

Our findings differed from those of a prior report in which cousin-comparison and post-birth IPI analyses suggested that an observed increased risk of ADHD with IPI <6 months was due primarily to confounding by familial factors. [24] This may be related to methodological differences or may reflect true differences between populations.

Conclusions

This study suggests that IPI <6 months or ≥60 months are associated with an increased risk of ADHD in the offspring. This adds to the existing evidence that both short and long IPI are associated with neurodevelopmental risks, and that these risks apply to outcomes more broadly than the previously well-documented associations with ASD. Additional investigation should be conducted to confirm this association and to elucidate the mechanisms behind it.

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Supporting Information

Figure 1. Odds ratios and 95% confidence intervals for the association between interpregnancy interval (IPI) and ADHD in Finnish births, 1991–2005. Estimated using a conditional logistic regression model adjusted for parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.

Table 1. Frequencies of characteristics of cases with attention-deficit/hyperactivity disorder (ADHD) and matched controls from Finnish Births, 1991–2005.

Covariate	Cases No. (%)	Controls No. (%)	OR (95% CI)[a]
Subject sex			--
Female	1538 (15.9)	5628 (16.1)	
Male	8152 (84.1)	29,348 (83.9)	
Maternal age (years)			
≤19	626 (6.5)	833 (2.4)	1.00 (Reference)
20-29	5365 (55.4)	17,517 (50.1)	0.40 (0.36, 0.45)
30-39	3438 (35.5)	15,621 (44.7)	0.29 (0.26, 0.32)
≥40	261 (2.7)	1005 (2.9)	0.34 (0.29, 0.41)
Paternal age (years) [b]			
≤19	203 (2.2)	199 (0.6)	1.00 (Reference)
20-29	4037 (43.1)	12,865 (37.2)	0.31 (0.25, 0.38)
30-39	4227 (45.1)	18,131 (52.4)	0.23 (0.19, 0.28)
≥40	900 (9.6)	3398 (9.8)	0.26 (0.21, 0.32)
Maternal parity [b]			
0	4377 (45.4)	13,793 (39.8)	1.00 (Reference)
1	3043 (31.5)	12,163 (35.1)	0.78 (0.74, 0.82)
2	1459 (15.1)	5835 (16.8)	0.78 (0.73, 0.84)
≥3	772 (8.0)	2888 (8.3)	0.85 (0.77, 0.92)
Parental psychiatric diagnosis [c]			
Both parents affected	832 (8.6)	899 (2.6)	1.00 (Reference)
Only mother affected	1488 (15.4)	3136 (9.0)	0.52 (0.47, 0.59)
Only father affected	1445 (14.9)	3410 (9.8)	0.46 (0.41, 0.51)
Neither affected	5925 (61.2)	27,531 (78.7)	0.23 (0.21, 0.26)
Maternal history of substance use disorder [d]			
No	7242 (74.7)	30,886 (88.3)	1.00 (Reference)
Yes	2448 (25.3)	4090 (11.7)	3.41 (3.06, 3.81)
Maternal marital status [b]			
Married/in relationship	7916 (92.6)	31,041 (96.8)	1.00 (Reference)
Single	629 (7.4)	1029 (3.2)	2.53 (2.26, 2.82)

Covariate	Cases No. (%)	Controls No. (%)	OR (95% CI)[a]
Maternal immigrant status			
Immigrated	231 (2.4)	553 (1.6)	1.00 (Reference)
Did not immigrate	9459 (97.6)	34,423 (98.4)	0.66 (0.56, 0.77)
Maternal education			
College/bachelor univ degree	1423 (14.7)	7778 (22.2)	1.00 (Reference)
Master/licenciate/doctorate	437 (4.5)	3534 (10.1)	0.68 (0.60, 0.76)
None after elementary	2889 (29.8)	5575 (15.9)	2.94 (2.72, 3.16)
Vocational/secondary graduate	4941 (51.0)	18,089 (51.7)	1.54 (1.44, 1.64)
Paternal education [b]			
College/bachelor univ degree	902 (9.6)	5467 (15.8)	1.00 (Reference)
Masters/licenciate/doctorate	443 (4.7)	3594 (10.4)	0.74 (0.66, 0.84)
None after elementary	3106 (33.2)	6860 (19.8)	2.79 (2.57, 3.04)
Vocational/secondary graduate	4916 (52.5)	18,672 (54.0)	1.62 (1.50, 1.75)
Birthweight (g)			
<2500	607 (6.3)	894 (2.6)	2.53 (2.28, 2.82)
≥2500	9038 (93.7)	33,778 (97.4)	1.00 (Reference)
Gestational age (weeks)			
<37	759 (7.9)	1582 (4.6)	1.79 (1.64, 1.96)
≥37	8854 (92.1)	33,002 (95.4)	1.00 (Reference)

[a] Based on unadjusted conditional logistic regression to account for matching.

[b] Observations were missing data for the following covariates: paternal age, n=706; maternal parity, n=336; maternal marital status, n=4051; paternal education, n=706; birthweight, n=349; gestational age, n=469.

[c] Lifetime ICD-10 diagnoses of F10–F99, excluding F70-F79; or the corresponding diagnoses based on the ICD-9 [291–316; excluding 293-294] and the ICD-8 [291–309; 292-294]. Substance abuse disorders (see below) were also excluded.

[d] ICD-10: F10–19; ICD-9: 291–292, 303–305; and ICD-8: 291, 303, and 304).

Table 2. Odds ratios and 95% confidence intervals for the association between interpregnancy interval (IPI) and ADHD in Finnish births, 1991–2005.

Interpregnancy interval (months)	ADHD cases N (%)	Controls N (%)	Odds ratio (95% confidence interval)	
			Unadjusted (n=44,043)	Adjusted[a] (n=43,401)
<6	305 (3.2)	859 (2.5)	1.54 (1.33, 1.77)	1.30 (1.12, 1.51)
6-11	744 (7.8)	3131 (9.1)	1.01 (0.92, 1.12)	1.01 (0.91, 1.12)
12-23	1320 (13.8)	5947 (17.2)	0.95 (0.88, 1.03)	1.00 (0.92, 1.09)
24-59	1646 (17.2)	7052 (20.5)	1.00 (Reference)	1.00 (Reference)
60-119	872 (9.1)	2862 (8.3)	1.30 (1.18, 1.43)	1.12 (1.02, 1.24)
≥120	323 (3.4)	899 (2.6)	1.54 (1.34, 1.77)	1.25 (1.08, 1.45)
First-born, no IPI	4354 (45.5)	13,729 (39.8)	1.36 (1.28, 1.45)	1.34 (1.25, 1.44)

[a] Adjusted for: parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.

Table 3. Odds ratios and 95% confidence intervals for the association between interpregnancy interval (IPI) and ADHD in Finnish births, 1991–2005, adjusted for parental ages.

IPI	Age at prior birth[a] (N=16,096) OR (95% CI)	Age at current birth[b] (n=43,401) OR (95% CI)
<6 months	1.34 (1.12, 1.60)	1.25 (1.07, 1.45)
6-11 months	1.03 (0.92, 1.16)	0.98 (0.88, 1.08)
12-23 months	1.00 (0.91, 1.10)	0.98 (0.90, 1.06)
24-59 months	1.00 (Reference)	1.00 (Reference)
60-119 months	1.08 (0.97, 1.21)	1.17 (1.06, 1.30)
>=120 months	1.15 (0.97, 1.36)	1.37 (1.18, 1.60)
First born, no IPI	excluded	1.23 (1.15, 1.32)

[a] Adjusted for maternal age at previous birth. Also adjusted for parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.

[b] Adjusted for maternal age and paternal age at the current birth. Also adjusted for parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.

Table 4. Odds ratios and 95% confidence intervals for the association between interpregnancy interval (IPI) and ADHD, stratified by the co-morbid diagnosis of autism spectrum disorder (ASD) in the case.

Interpregnancy interval (months)	Co-morbid ASD diagnosis in the case (N=5238) OR[a] (95% CI)	No ASD diagnosis in the case (N=38,163) OR[a] (95% CI)	$P_{interaction}$[b]
<6	0.34 (0.14, 0.83)	1.32 (1.13, 1.55)	0.003
6-11	0.80 (0.42, 1.50)	1.00 (0.90, 1.11)	0.49
12-23	0.62 (0.37, 1.05)	1.01 (0.92, 1.10)	0.07
24-59	1.00 (Reference)	1.00 (Reference)	--
60-119	0.76 (0.41, 1.39)	1.11 (1.00, 1.23)	0.23
≥120	1.24 (0.51, 3.01)	1.18 (1.00, 1.38)	0.91
First-born, no IPI	1.06 (0.69, 1.64)	1.29 (1.20, 1.39)	0.38

[a] Adjusted for parental psychiatric diagnosis, maternal history of substance abuse, maternal immigration, maternal education, and paternal education.
[b] $P_{int,}$ p-value for interaction.