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Outcome-dependent associations between short interpregnancy interval and offspring psychological and educational problems: A population-based quasi-experimental study

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Abstract

Background: Causal interpretation of associations between short interpregnancy interval, the duration from the preceding birth to the conception of the next-born index child, and offspring's psychological and educational problems may be influenced by a failure to account for unmeasured confounding.

Methods: Using population-based Swedish data from 1973-2009, we estimated the association between interpregnancy interval and outcomes (autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), severe mental illness, suicide attempt, criminality, substance use problem, and failing grades) while controlling for measured covariates. We then used cousin-comparisons, post-birth intervals (the interval between the second- and third-born siblings to predict second-born outcomes), and sibling-comparisons, to assess the influence of unmeasured confounding. We included an exploratory analysis of long interpregnancy interval.

Results: Interpregnancy intervals of 0-5 and 6-11 months were associated with higher odds of outcomes in cohort analyses. Magnitudes of association were attenuated following adjustment for measured covariates. Associations were eliminated for ADHD, severe mental illness, and failing grades, but maintained magnitude for ASD, suicide attempt, criminality, and substance use problem in cousin-comparisons. Post-birth interpregnancy interval and sibling-comparisons suggested some familial confounding. Associations did not persist across models of long interpregnancy interval.

Conclusions: Attenuation of the association in cousin-comparisons and comparable post-birth interval associations suggests that familial genetic or environmental confounding accounts for a majority of the association for ADHD, severe mental illness, and failing grades. Modest associations appear independent of covariates for ASD, suicide attempt, criminality, and

substance use problem. Post-birth analyses and sibling-comparisons, however, show some confounding in these associations.

MeSH terms and Keywords: pregnancy interval, birth spacing, psychopathology, case-comparison studies, interpregnancy interval

Key Messages

- Previous research asserts a causal association between short interpregnancy interval and offspring psychopathology. However, several alternative hypotheses may better explain the associations between short interpregnancy interval and adverse offspring outcomes.
- The current paper includes a series of traditional cohort analyses, cousin-comparisons, post-birth interpregnancy interval negative control analyses, and sibling-comparisons to examine the pattern of associations.
- For all studied outcomes, measured and unmeasured genetic or environmental confounding is present in the associations with short interpregnancy interval.
- Associations between short interpregnancy interval and ADHD, severe mental illness, and failing grades are fully explained by familial genetic or environmental confounding, while associations with ASD, suicide attempt, criminality, and substance use problem show modest independent associations, though confounding is still present.

Several recent studies have suggested that short interpregnancy interval, or the duration from the preceding birth to the conception of the next-born index child, can lead to major long-term problems, including mental illness and low academic achievement [1-7]. For example, an interpregnancy interval of less than 6 months is associated with a 300% elevated risk for offspring autism spectrum disorder (ASD) [2] and a 150% elevated risk for schizophrenia [1, 3]. A causal relation between short interpregnancy interval and these burdensome outcomes is compelling because interpregnancy interval is a relatively modifiable risk factor [8]. Further, there are plausible causal mechanisms whereby a short interpregnancy interval may not allow for adequate restoration of the maternal nutritional foundation, especially of the fetal growth-relevant micronutrient folate [9]. As such, negative effects of short interpregnancy interval could be reduced with a simple maternal folic acid supplement [10].

More research is needed before resources are directed towards altering interpregnancy interval for targeted prevention of offspring psychological and educational outcomes, however [11]. Traditional studies that compare outcomes across unrelated individuals may be confounded by genetic or environmental factors that influence both interpregnancy interval and the outcome [5]. Potential confounding factors include maternal socioeconomic variables, ethnicity, race, education, smoking status, and maternal age [12-16]. Additionally, within adolescent mothers, poor mental health, trauma history, and behavioral aggression correlate with shorter interpregnancy intervals [13, 17]. Therefore, causal claims from traditionally-designed studies [5, 6] should be made with caution. Previous studies have also been limited by skewed measurement of interpregnancy interval (i.e., birth to birth rather than birth to conception) [1, 7], which confounds spacing with gestational age, a factor that influences both interpregnancy interval [18], as well as the likelihood of offspring psychopathology [19].

Family-based designs are well equipped to explore alternative explanations to causal claims [20-22]. Family-based designs that compare related individuals, such as cousins, have the ability to control for all factors that make those individuals similar. This is important when examining an exposure that may be highly influenced by genetic or environmental factors [23]. While sibling-comparisons offer greater control of unmeasured genetic and environmental influences but are problematic in relation to the nature of the exposure (i.e., interpregnancy interval); the first-born does not have an interpregnancy interval, there may be birth-order effects, and the first-born's outcomes may impact the interval prior to conception of the second-born. Therefore, cousin-comparisons may be a better-suited study design [24] to offer some control of unmeasured genetic factors (cousins share 12.5% of their genetic makeup on average) while avoiding the design issues of sibling-comparisons.

Another way to explore alternative explanations (e.g., family culture contributing to both short interpregnancy intervals and increased likelihood of childhood behavior disorders) is with a negative control design wherein the interpregnancy interval to the following (next-born) sibling is used to predict the outcome of the prior-born sibling. Since any association with this *post-birth interval* cannot be due to the pregnancy-related mechanisms through which interpregnancy interval theoretically functions, it may be taken to indicate a role of familial confounding, genetic or environmental [1]. If, on the other hand, there is no association between post-birth interval and the prior-born's outcomes while there is a robust association between the prior interpregnancy interval and the outcome, then there is support for an independent association. Two studies have published significant associations between post-birth interval and psychological outcomes. One study found that schizophrenia was predicted from both the offspring's interpregnancy interval

and post-birth interval [1] and another study showed that short post-birth intervals were associated with elevated risk of psychotic disorder [7], both suggestive of confounding.

The current study used one of the largest, longitudinal, population-based databases in the world, the Swedish population registers, to examine the risk conferred by short interpregnancy interval on several offspring psychological and educational problems. Outcomes included ASD, attention-deficit/hyperactivity disorder (ADHD), severe mental illness, suicide attempt, criminality, substance use problem, and failing grades. To examine the influence of confounding, the current study utilized cousin-comparisons and post-birth interpregnancy intervals. We further examined familial confounding by performing sibling-comparisons in sensitivity analyses. In addition, we included an exploratory analysis of the impact of long interpregnancy interval on these outcomes, as very little work has been performed examining this factor [6].

Methods

Study population

The institutional review board at Indiana University and the Regional Ethical Review Board in Stockholm approved this study. We first identified offspring and their mothers using the Swedish Medical Birth Register, which provided data on more than 96% of births in Sweden since 1973 [25]. After identifying fathers using the Multi-Generation Register [26] we then collected information on several parental characteristics and offspring outcomes from the following registers: (1) the National Crime Register provided information on criminal convictions since 1973 [27], (2) the National Patient Register provided diagnoses for psychopathological and substance-related inpatient hospital admissions since 1973 [28], (3) the National School Register provided information on offspring school grades beginning in 1983; (4)

the Education Register provided information on highest level of completed formal education through 2009; and (5) the Migration Register and the (6) Cause of Death Register provided information important in determining the censoring information.

The initial population included live birth-related information for 3 403 185 individuals with valid maternal identifiers born between 1973 and 2008. The number of individuals removed for exclusionary reasons are listed in the data flow chart presented as Figure 1. We used a complete case analysis given the mechanisms for missing data are not fully understood [29]. The final cohort for main-analyses consisted of 1 050 271 second-born and 368 549 third-born offspring. There were 784 640 distinct maternal-side grandmothers represented in the cohort used in cousin-comparison models and 497,066 distinct cousins. Post-birth interval analyses only included the 346 739 individuals who had third-born siblings and sibling-comparison analyses use all second- and third-born siblings. For childhood outcomes of ADHD and ASD, years of birth were limited to 1987 through 2007 in order to capture the highest-quality inpatient and outpatient diagnosis data (N=973 391).

[Insert Figure 1 here]

Measures

Interpregnancy interval

We defined interpregnancy interval as the number of completed months between the birth of the preceding (earlier-born) offspring and the date of conception of the index (next-born) offspring. Date of conception was obtained from information on gestational age at birth estimated from last menstrual period or ultrasound. We treated the second-born offspring as the index offspring. To allow prediction also by their post-birth interpregnancy interval, we used the subsample of second-born offspring that had a third sibling interpregnancy interval from the

birth of the second-born to the conception of the third-born. We categorized interpregnancy intervals as 0 to 5 months, 6 to 11 months, 12 to 23 months, and 24 to 35 months (referent).

Offspring outcomes

Outcomes were chosen because of previously indicated positive associations with the risk factor, biological relatedness to the previously studied outcomes, normative indicators of decreased functioning, and resource costliness [1-7]. All clinical diagnoses were according to the year-dependent ICD- 8, -9, and -10 codes as appropriate. ICD codes are presented in the Supplementary Material Table 1A. Follow-up for each outcome was through 2009.

We defined *ASD* as including pervasive developmental disorder, disintegrative psychosis, Heller's syndrome, and schizophrenic syndrome of childhood [30]. We defined *ADHD* according to hyperkinetic and attention deficit hyperactivity disorder diagnoses [31]. For both childhood outcomes, offspring had to have been at least 2 years old at the time of diagnosis. Data for *ASD* and *ADHD* included inpatient psychiatric diagnosis beginning in 1987 and outpatient specialist diagnosis beginning in 2001 [30, 32] through 2007. We defined *severe mental illness* as measured by the age at the first inpatient hospitalization for bipolar disorder, broadly defined schizophrenia, or other nonorganic psychotic disorders [33]; *suicide attempt* as indicated by the age at first attempt recorded in inpatient care records as the primary or secondary reason for care [34], *criminality*, according to the age at first occurrence of any criminal conviction under the Swedish Penal code, beginning at age 15, the Swedish age of legal responsibility [35]; and *substance use problem*, according to first inpatient hospitalization involving a primary or secondary diagnosis of alcohol- or any other, non-nicotine, substance use disorder [36]. We also defined *failing grades* according to summary grades in grade nine [37]. Summary grade scores were calculated by summing the numeric value of grades across 16 different subjects (pass = 10,

pass with distinction = 15, and pass with honors = 20) for a maximum summary grade of 320. A score of 160 indicated that the mean across the 16 grades was only at “pass”; any score below this was used as an indicator for failing grades [37]. The minimum age for all adult psychopathology outcomes was 12 years old except for criminality. Those born from 1973 to 1997 were informative for all adult outcomes except for criminality in which those born 1973 to 1994 were informative. Outcome-dependent sample information is presented in Table 1.

[Table 1 here]

Measured covariates

We included various measured covariates depending on the statistical model. We chose covariates based on their correlations with interpregnancy interval and psychopathological outcomes [19]. See Supplementary Material Table 2A for associations between interpregnancy interval and measured covariates in our sample. Measured covariates included maternal and paternal age at the index birth, highest education level, nationality, and if the earlier-born offspring had a different biological father. Some adjusted models also included measured lifetime parental psychopathology. In particular, we included parental criminality as indexed by any criminal conviction under the Swedish Penal code beginning at age 15, the Swedish age of legal responsibility [35, 38], substance use problem defined as an inpatient hospitalization involving a primary or secondary diagnosis of alcohol- or any other, non-nicotine, substance use disorder [39], suicide attempt as indicated by an attempt recorded in inpatient care records as the a primary or secondary reason for care [34], and severe mental illness as measured by an inpatient hospitalization for bipolar disorder, broadly defined schizophrenia, or other nonorganic psychotic disorders [33]. Except for criminality, the minimum age for all parental mental health

outcomes was 12 years old. All clinical diagnoses were according to ICD versions 8, 9, and 10 and are presented in Supplementary Material Table 1A.

Statistical analyses

We used Cox survival analyses for right-censored outcomes (e.g., attempted suicide) and logistic regression analyses for dichotomous outcomes (i.e., failing grades) when predicting the second-born, index offspring's outcomes. For the survival analyses, if the offspring had not received a diagnosis within the study period, they contributed person-time at risk until death, emigration, or the end date of follow-up (December 31, 2009), whichever came first.

A series of models were performed for each outcome. Model 1 was a baseline model that only adjusted for offspring sex and year of birth. Model 2 adjusted for offspring sex, year of birth, and maternal and paternal age, highest education, nationality, and if the fathers were different. Model 3 additionally adjusted for parental psychopathology variables including maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness.

In Model 4, we limited the sample to maternal cousins with different interpregnancy interval categories and used fixed-effects modeling or conditional logistic regression. In other words, a risk for outcome in second-born offspring was compared with their second-born maternal cousin with a differing interpregnancy interval category. Model 4 additionally included all covariates in Model 3.

Model 5 used post-birth interpregnancy interval (the interval between the second- and third-born offspring within a family) to predict second-born outcomes in the subsample that had a third sibling [1]. This model also adjusted for the same measured covariates as in Models 3 and 4. Again, if a positive association is identified using post-birth interval, familial confounding is

implicated. If there is no association between post-birth interval and the prior-born's outcomes, then an independent and unique association with interpregnancy interval may be warranted given other results.

Sensitivity analysis

We also performed a sibling-comparison in an effort to use a family-based design with different assumptions than the cousin-comparison design while continuing to control for unmeasured environmental and genetic factors that may influence the relation. For this analysis, interpregnancy interval was calculated between the first- and second-born (for the second-born) as well as between the second- and third-born offspring (for the third-born); Second- and third-born offspring outcomes were compared in a model that also adjusted for measured covariates that may have varied between siblings (i.e., offspring sex, birth year, parity, and different father).

We also examined associations following long interpregnancy intervals. In particular, as compared with a reference category of 24-35 months, we examined outcomes associated with interpregnancy intervals of 36 to 71 months and 72 or more months across all models used in the main analyses (i.e., baseline and adjusted, cousin-comparisons, and post-birth analyses).

Results

Table 2 presents demographic information for the second-born offspring.

[Table 2 here]

Odds and hazard ratios predicting all studied outcomes can be seen in Table 3. In the baseline models, an interpregnancy interval of 0-5 months was associated with higher odds of every studied outcome; the baseline associations were moderate and varied from HR=1.38 (95% CI=1.22-1.56) for ADHD and HR=1.70 (95% CI=1.44-2.00) for ASD when compared with interpregnancy interval of 24-35 months. Across outcomes, magnitudes of association were

minimally attenuated following adjustment for measured covariates in Model 2. The associations were moderately to greatly attenuated, for the shortest interpregnancy interval in Model 3 where parental psychopathology measures were included as measured covariates.

In Model 4, in which second-born cousins with varying interpregnancy intervals were compared, associations were fully attenuated for ADHD (HR=1.16, 95% CI=0.82-1.63), severe mental illness (HR=1.04, 95% CI=0.64-1.69), and failing grades (HR=1.12, 95% CI=0.97-1.30). For ASD (HR=1.63, 95% CI=1.04-2.55), suicide attempt (HR=1.34, 95% CI=1.01-1.79), and criminality (HR=1.18, 95% CI=1.08-1.28), moderate associations persisted. The magnitude of association remained elevated for substance use problem (HR=1.20, 95% CI=0.98-1.45), though confidence intervals were large.

In Model 5, post-birth intervals (i.e., the interval between the second- and third-born offspring) were associated with higher odds of all outcomes but substance use problem, suggesting the presence of familial confounding. In other words, the length of interval after the birth of the second-born offspring to the next sibling's conception significantly predicted the outcomes of the second-born offspring.

[Table 3 here]

Sensitivity and Exploratory Analyses

Sibling-comparison

Outcome rates of the second and third-born siblings were compared if their interpregnancy intervals differed; the subset included 569,802 differentially exposed sibling pairs. Results are presented in Supplementary Material Table 3A. In summary, after controlling for all factors that siblings share, there were no statistically significant associations or notably high magnitudes of association between short interpregnancy interval and the studied outcomes.

Long interpregnancy interval

We also explored the relation between long interpregnancy intervals and the studied outcomes. This was approached as an exploratory analysis, as little research has been done on this exposure, which is correlated with parental age. We examined 36-71 months and 72 or more months as compared to the reference range of 24-35 months. Supplementary Material Table 4A presents the results. For the longest interpregnancy interval period, odds of all studied outcomes were higher compared with the reference interval period (24-35 months) in the baseline model. These associations, however, were dramatically attenuated following covariate adjustment and none remained in the cousin-comparisons. There were also weak associations between post-birth interpregnancy intervals and ADHD, suicide attempt, criminality, substance use problem, and failing grades; supporting the interpretation that associations with these outcomes may largely be due to familial confounding.

Discussion

Using a Swedish population cohort, we explored the relation between interpregnancy interval and offspring psychological and educational problems, particularly problems associated with substantial morbidity and previously shown to be associated with short interpregnancy interval. Our findings suggest that much, if not all, of the association between short interpregnancy interval and elevated risk for offspring child and adult psychological and educational outcomes identified in general samples are due to genetic or shared environmental confounding. While our baseline and adjusted findings are in agreement with previous research reporting associations between short interpregnancy interval and ASD, severe mental illness, and academic performance [1-7], the more rigorous examination in the current study including

within-family and post-birth analyses does not support causal interpretations. However, the pattern of association is outcome-specific. For ADHD, severe mental illness, and failing grades, the association was fully attenuated in cousin- and sibling-comparisons and post-birth analyses supported familial confounding. For ASD, suicide attempt, criminality, and substance use problem, elevated magnitudes of association were maintained through cousin-comparisons, with wider confidence intervals than in previous models. This supports a modest independent effect even when controlling for all factors that make cousins similar to each other. Post-birth and sibling-comparison analyses, however, suggested familial confounding was present even for these maintained associations.

Others have applied a sibling “case-comparison” approach to study these associations, and our results differ from their conclusions. This may be because the previous projects used the first and second-born offspring, as compared with our use of cousins and the second- and third-born offspring in sibling-comparisons [2, 5]. We used cousins to remove birth order bias and bias introduced from prodromal symptoms emerging in the older-born sibling prior to the birth or diagnosis of the second-born [2, 5]. In our sibling-comparisons, we did not include first-borns because they do not have a prior interpregnancy interval. An additional design difference is that previous studies examined rates of ASD in the second sibling across different interpregnancy interval categories, given that the first sibling had *not* been diagnosed with ASD [2, 5]. Future research might include direct comparison of these approaches.

For our exploratory analysis of long interpregnancy intervals, the population-wide associations were fully attenuated by adjustment (measured covariates and cousin-comparisons). Post-birth analyses showed modest positive association between the longest interpregnancy intervals and suicide attempt, criminality, substance use problem, and failing grades. Given the

attenuation of the associations throughout the traditional and cousin-comparison analyses, this elevation in post-birth analyses may indicate familial confounding. As stated, previous work on long interpregnancy interval is limited [6]. Most previous work has grouped any interpregnancy interval over 37 [3] or 45 months [1] together and/or treated the group as the reference category [2, 5], thereby limiting the conclusions that could be drawn. Our results should also be interpreted with caution as long-interpregnancy interval is correlated with older parental age and may be associated with infertility, maternal infection, and breastfeeding (and therefore a longer period of maternal nutrient depletion) [1, 8, 10, 36, 40]. In addition, the long interpregnancy interval may be due to the older-born offspring's early-manifesting psychological outcomes. More research on the ramifications of long interpregnancy interval is needed.

We were able to draw our conclusions by utilizing several designs that account for unmeasured confounding with differing assumptions and limitations in a large sample. The family-based designs of cousin-comparison, and sibling-comparison in sensitivity analyses, enabled us to account for unmeasured environmental and genetic factors shared by cousins or siblings that may influence the associations. The cousin-comparison approach removed the problems associated with comparing outcomes across siblings where the first-born did not experience an interpregnancy interval and three-child families are required. We also performed a post-birth interval analysis to examine alternative hypotheses. Despite these strengths, important limitations must be considered. First, due to the relative ethnic homogeneity of the Swedish population, future analyses across ethnic and racial groups is needed because interpregnancy intervals vary across these groups [12, 14, 15]. Similarly, prenatal care is advanced and comprehensive in Sweden and may have influenced interpregnancy interval length [41]. Second, we cannot rule out the possibility that “stoppage”, or the decision to not have a second child due

to diagnosis (e.g., ASD) in the first child, may have influenced family structure. If these families were not included in the sample because they did not have a second child, our estimates may be biased because of the non-inclusion of a subgroup with high familial risk for certain disorders. Third, every design has inherent limitations and assumptions, such as shared characteristics across cousins, [21] and family-based designs are not randomized controlled studies; therefore, we cannot rule out all possible confounding factors. Further, confidence intervals became wider as the sample was more limited by relatedness. By combining multiple designs, however, we hope to triangulate on the “real” association. Finally, there may be some interpregnancy interval length category exposure misclassification because of conception date error. In addition, we were unable to identify spontaneous or induced abortions [42], which may have influenced interpregnancy interval length.

Our findings suggest that associations of short interpregnancy interval and elevated offspring psychological and educational problems are modest and outcome-dependent. Familial factors, either shared genetic or environmental, appear to play a role in these associations [11-17].

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Table 1. Kaplan-Meier estimates and sample details by outcome and interpregnancy interval category.

Outcome	Birth year	n cases	Total N	Interpregnancy Interval (months)							
				0-5		6-11		12-23		24-35	
				n	KME (n %)	n	KME (n %)	n	KME (n %)	n	KME (n %)
ASD	1987-2007	6 112	973 391	260	1.80	895	1.38	1 744	1.07	943	1.08
ADHD	1987-2007	11 945	973 391	449	3.42	1 539	2.60	3 295	2.16	1 945	2.27
Severe Mental Illness	1973-1997	6 162	957 099	234	1.99	756	1.87	1 712	1.49	1 206	1.36
Suicide Attempt	1973-1997	11 247	957 099	485	3.22	1 430	2.53	3 136	2.01	2 311	1.97
Criminality	1973-1994	99 452	824 200	4 299	23.81	12 658	18.81	29 662	16.13	21 029	15.56
Substance Use Problem	1973-1997	17 512	957 099	745	4.70	2 282	3.95	5 093	3.13	3 398	2.85
Failing Grades	1973-1997	99 917	957 099	4 333	(21.08)	12 026	(14.94)	28 414	(13.23)	20 637	(13.53)

Note: KME=Kaplan-Meier product-limit survival estimate percentage at 20 (ASD, ADHD) or 30 years (all other outcomes). KMEs were not calculated for failing grades because it is a logistic outcome. Numbers across interpregnancy interval categories do not add to n cases because data for long interpregnancy interval categories (i.e., 36-71 and 72+ months) are not included in this presentation.

Table 2. Descriptive characteristics and covariates for n=1,050,271 (74%) index, second-born offspring in the sample of n=1,418,820.

Variable	n (%)
Second-born offspring	1 050 271
Interpregnancy Interval (months)	
0-5	27 888 (2.7)
6-11	128 096 (12.2)
12-23	369 173 (35.2)
24-35*	233 983 (22.3)
36-71	216 631 (20.6)
72+	74 500 (7.1)
Maternal Age (yrs)	
< 20	6618 (0.6)
20-29*	596101 (56.8)
30-39	433634 (41.3)
≥ 40	13918 (1.3)
Paternal Age (yrs)	
< 20	1299 (0.1)
20-29*	390057 (37.1)
30-39	576730 (54.9)
≥ 40	82185 (7.8)
Highest Maternal Education	
≤ 9 years primary and lower secondary*	17979 (1.7)
9 years primary and lower secondary	88677 (8.4)
3 years upper secondary	514757 (49.0)
Post-secondary/and or postgraduate	428858 (40.8)
Highest Paternal Education	
≤ 9 years primary and lower secondary*	43960 (4.2)
9 years primary and lower secondary	131470 (12.5)
3 years upper secondary	528773 (50.4)
Post-secondary/and or postgraduate	346068 (33.0)
Mother of Swedish Nationality	933506 (88.9)
Father of Swedish Nationality	926035 (88.2)
First- and Second-born to Different Fathers	93379 (8.9)
Maternal Psychopathology	
Criminality	109882 (10.5)
Attempted suicide	23099 (2.2)
Substance use problem	17300 (1.7)
Severe mental illness	8378 (0.8)
Paternal Psychopathology	
Criminality	393941 (37.5)
Attempted suicide	16520 (1.6)
Substance use problem	33079 (3.2)
Severe mental illness	6140 (0.6)

Note: * denotes reference category for model estimation.

Table 3. Hazard or odd ratios predicting child and adult psychopathology across interpregnancy interval and model.

Outcome and model	Interpregnancy Interval (months)										Ref
	0-5			6-11			12-23			24-35	
	HR/OR	95% CI		HR/OR	95% CI		HR/OR	95% CI			
ASD											
Model 1	1.70	1.44	2.00	1.35	1.22	1.50	0.99	0.90	1.08		Ref
Model 2	1.63	1.38	1.93	1.38	1.25	1.54	1.03	0.94	1.12		Ref
Model 3	1.59	1.34	1.87	1.37	1.23	1.52	1.03	0.94	1.12		Ref
Model 4 / Cousin-comparison	1.63	1.04	2.55	1.38	1.05	1.80	1.06	0.83	1.35		Ref
Model 5 / Post-birth	1.50	1.15	1.94	1.29	1.08	1.54	1.12	0.96	1.31		Ref
ADHD											
Model 1	1.38	1.22	1.56	1.05	0.97	1.14	0.90	0.84	1.14		Ref
Model 2	1.29	1.14	1.47	1.09	1.01	1.18	0.95	0.89	1.01		Ref
Model 3	1.18	1.04	1.34	1.06	1.98	1.14	0.95	0.89	1.01		Ref
Model 4 / Cousin-comparison	1.16	0.82	1.63	0.95	0.77	1.18	0.84	0.70	1.00		Ref
Model 5 / Post-birth	1.27	1.05	1.54	0.99	0.87	1.14	1.00	0.89	1.13		Ref
Severe Mental Illness											
Model 1	1.61	1.37	1.88	1.45	1.31	1.60	1.18	1.09	1.27		Ref
Model 2	1.51	1.29	1.77	1.43	1.29	1.58	1.18	1.09	1.28		Ref
Model 3	1.32	1.13	1.55	1.34	1.22	1.49	1.17	1.08	1.27		Ref
Model 4 / Cousin-comparison	1.04	0.64	1.69	1.05	0.81	1.36	0.88	0.72	1.08		Ref
Model 5 / Post-birth	1.46	1.12	1.90	1.32	1.11	1.57	1.12	0.97	1.30		Ref
Suicide Attempt											
Model 1	1.67	1.49	1.87	1.30	1.21	1.40	1.00	0.94	1.06		Ref
Model 2	1.48	1.32	1.65	1.28	1.19	1.34	1.01	0.95	1.07		Ref
Model 3	1.26	1.13	1.42	1.19	1.11	1.29	0.99	0.93	1.05		Ref
Model 4 / Cousin-comparison	1.34	1.01	1.79	1.20	1.01	1.42	1.03	0.89	1.18		Ref
Model 5 / Post-birth	1.19	0.98	1.44	1.14	1.00	1.30	0.99	0.89	1.10		Ref
Criminality											
Model 1	1.62	1.56	1.69	1.24	1.21	1.27	1.04	1.02	1.06		Ref
Model 2	1.40	1.34	1.45	1.21	1.18	1.24	1.05	1.03	1.07		Ref
Model 3	1.25	1.20	1.30	1.15	1.12	1.18	1.03	1.01	1.05		Ref
Model 4 / Cousin-comparison	1.18	1.08	1.28	1.04	0.99	1.10	1.01	0.97	1.06		Ref
Model 5 / Post-birth	1.20	1.12	1.29	1.11	1.06	1.16	1.03	0.99	1.07		Ref
Substance Use Problem											
Model 1	1.65	1.50	1.81	1.34	1.26	1.42	1.11	1.06	1.17		Ref
Model 2	1.46	1.33	1.60	1.32	1.24	1.40	1.12	1.07	1.18		Ref
Model 3	1.25	1.14	1.37	1.23	1.16	1.31	1.11	1.05	1.16		Ref
Model 4 / Cousin-comparison	1.20	0.98	1.45	0.93	0.82	1.05	1.07	0.97	1.19		Ref
Model 5 / Post-birth	1.08	0.91	1.27	1.15	1.03	1.28	1.02	.93	1.11		Ref

Failing Grades

Model 1	1.69	1.62	1.77	1.10	1.07	1.13	0.97	0.95	0.99	Ref
Model 2	1.36	1.30	1.42	1.10	1.06	1.13	1.00	0.98	1.02	Ref
Model 3	1.19	1.14	1.25	1.03	1.00	1.06	0.98	0.96	1.01	Ref
Model 4 / Cousin-comparison	1.12	0.97	1.30	0.97	0.86	1.09	0.98	0.88	1.08	Ref
Model 5 / Post-birth	1.23	1.14	1.33	1.15	1.09	1.21	1.08	1.03	1.12	Ref

Note: Number of differentially exposed cousin pairs included n = 338,604, Post-IPi sample included n = 346,739, Models were adjusted for the following measured covariates: *Model 1*: offspring sex, year of birth; *Model 2*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers; *Model 3*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers, maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness; *Model 4 / Cousin-comparison*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers, maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness; *Model 5 / Post-birth interpregnancy interval*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers, maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness, first-born preterm birth, low birth weight, and small for gestational age. Model 5 Predicts the second-born's outcomes from the post-birth interpregnancy interval (interval between second-born and third-born) in a subsample of families with three children. Follow-up through 2009.

Supplementary Material: Outcome-dependent associations between short interpregnancy interval and offspring psychological and educational problems: a population-based quasi-experimental study

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Table 1A. International Classification of Disease (ICD) version and codes used to measure psychological and substance use outcomes.

Outcome	Data Source	ICD Version	ICD Codes	Description
ASD	NPR	9, 10	299, F84	Includes disintegrative psychosis, Heller's syndrome, and schizophrenic syndrome of childhood
ADHD	NPR	9, 10	314, F90	Hyperkinetic syndrome and attention-deficit hyperactivity disorders
Severe mental illness	NPR	8, 9, 10	295, F20	Schizophrenia
			296.1, 296.3, 296A-296E, 296W, F30-F31	Bipolar disorder
			291, 292, 296.0, 296.2, 296.9, 297-299, 296B, 296X, F32.3 x.5 in F10-F19	Other non-organic psychoses
Suicide attempt	NPR	8, 9, 10	E950-E959, E980-E989, X60-X84, Y870, Y10-Y34, Y872	Certain and uncertain attempts including violent, non-violent, and other
Criminality	NCR	NA	NA	Earliest conviction for any criminal act, minimum age of 15 years
Substance use problem	NPR	8, 9, 10	303, 304, 305A, 305X, F10 (except x.5), F11-F19 (except x.5)	Alcohol or drug use (excludes nicotine) conviction

Note: ASD= Autism spectrum disorder, ADHD = attention-deficit/hyperactive disorder, NCR = National crime register, NPR = National patient register

Table 2A. Baseline and adjusted odds ratios of parental psychopathology, substance use, family characteristics, and first-born birth characteristics predicting interpregnancy interval prior to second-born offspring.

	Interpregnancy Interval (months)										
	0-5		6-11		12-23	24-35		36-71		72+	
	Baseline ^a	Adjusted ^b	Baseline ^a	Adjusted ^b		Baseline ^a	Adjusted ^b	Baseline ^a	Adjusted ^b	Baseline ^a	Adjusted ^b
Maternal Psychopathology											
Criminal conviction	1.71 (1.65-1.79)	1.41 (1.36-1.47)	1.27 (1.24-1.30)	1.21 (1.18-1.24)	ref	1.00 (0.98-1.02)	0.99 (0.97-1.01)	1.43 (1.40-1.46)	1.36 (1.33-1.39)	2.54 (2.48-2.60)	2.39 (2.33-2.46)
Suicide attempt	2.20 (2.00-2.41)	1.75 (1.59-1.92)	1.48 (1.39-1.57)	1.38 (1.30-1.47)	ref	1.04 (0.98-1.10)	1.05 (0.99-1.11)	1.70 (1.62-1.79)	1.71 (1.62-1.80)	3.28 (3.10-3.46)	3.52 (3.31-3.74)
Substance use problem	2.71 (2.38-3.08)	2.16 (1.89-2.47)	1.45 (1.33-1.60)	1.37 (1.25-1.50)	ref	1.04 (0.95-1.13)	1.04 (0.96-1.14)	1.79 (1.66-1.93)	1.76 (1.63-1.91)	4.07 (3.77-4.07)	4.28 (3.93-4.67)
Severe mental illness	1.66 (1.37-2.01)	1.79 (1.48-2.18)	1.23 (1.09-1.38)	1.27 (1.13-1.44)	ref	1.14 (1.03-1.26)	1.05 (0.95-1.17)	1.82 (1.66-1.99)	1.46 (1.33-1.60)	3.54 (3.20-3.92)	2.19 (1.96-2.44)
Paternal Psychopathology											
Criminal conviction	1.61 (1.57-1.65)	1.31 (1.28-1.34)	1.19 (1.17-1.65)	1.13 (1.12-1.15)	ref	1.00 (0.99-1.01)	0.99 (0.98-1.01)	1.24 (1.22-1.25)	1.22 (1.21-1.23)	1.67 (1.64-1.70)	1.74 (1.71-1.77)
Suicide attempt	2.29 (2.05-2.56)	1.85 (1.66-2.07)	1.45 (1.35-1.56)	1.37 (1.28-1.48)	ref	1.05 (0.98-1.13)	1.04 (0.97-1.11)	1.51 (1.42-1.61)	1.41 (1.32-1.51)	2.56 (2.38-2.75)	2.36 (2.18-2.56)
Substance use problem	2.56 (2.33-2.81)	2.06 (1.88-2.26)	1.43 (1.34-1.53)	1.36 (1.27-1.45)	ref	1.09 (1.03-1.16)	1.06 (1.00-1.13)	1.71 (1.62-1.80)	1.56 (1.48-1.65)	3.31 (3.12-3.51)	2.99 (2.80-3.19)
Severe mental illness	2.15 (1.84-2.51)	1.82 (1.55-2.13)	1.56 (1.41-1.72)	1.50 (1.35-1.66)	ref	0.99 (0.90-1.10)	0.94 (0.85-1.03)	1.50 (1.38-1.64)	1.24 (1.13-1.35)	2.47 (2.23-2.74)	1.72 (1.54-1.93)
Family structure and First-born factors											
Maternal first birth as teenager	2.05 (1.96-2.14)	1.54 (1.48-1.62)	1.18 (1.15-1.22)	1.11 (1.07-1.14)	ref	1.02 (0.99-1.05)	0.97 (0.94-0.99)	1.40 (1.37-1.44)	1.18 (1.15-1.21)	2.63 (2.55-2.71)	2.02 (1.96-2.08)
Different father than 1st born	0.94 (0.85-1.05)	0.74 (0.67-0.82)	0.64 (0.60-0.68)	0.58 (0.55-0.62)	ref	2.63 (2.54-2.72)	2.88 (2.79-2.98)	12.44 (12.09-12.80)	16.51 (16.03-17.00)	89.89 (87.23-92.63)	197.64 (191.06-204.44)
First-born preterm	2.49 (2.40-2.59)	2.43 (2.34-2.52)	1.15 (1.12-1.18)	1.15 (1.12-1.18)	ref	1.04 (1.02-1.07)	1.04 (1.01-1.06)	1.13 (1.10-1.15)	1.11 (1.08-1.13)	1.21 (1.17-1.25)	1.14 (1.10-1.18)
First-born low birth weight	3.18 (3.06-3.31)	3.04 (2.91-3.16)	1.24 (1.20-1.28)	1.23 (1.19-1.27)	ref	1.05 (1.02-1.07)	1.16 (1.13-1.19)	1.24 (1.20-1.27)	1.16 (1.13-1.19)	1.37 (1.32-1.42)	1.17 (1.12-1.22)
First-born small for gestational age	2.33 (2.23-2.44)	2.17 (2.07-2.27)	1.15 (1.12-1.19)	1.14 (1.10-1.18)	ref	1.06 (1.03-1.09)	1.03 (1.00-1.06)	1.28 (1.32)	1.17 (1.19-1.29)	1.56 (1.50-1.62)	1.27 (1.22-1.32)

^aModel adjusted for offspring sex and birth year; ^bModel additionally adjusted for maternal (except for maternal first birth as teenager) and paternal age at second-born's birth, highest level of education, and nationality.

Table 3A. Hazard or odds ratios from sibling-comparison predicting offspring outcomes from short interpregnancy intervals across increasingly rigorous models.

Outcome variable	Interpregnancy Interval (months)									
	0-5			6-11			12-23			24-35
	HR/OR	95% CI		HR/OR	95% CI		HR/OR	95% CI		
ASD	0.76	0.54	1.07	0.79	0.62	1.01	0.76	0.61	0.95	Ref
ADHD	0.83	0.64	1.07	0.92	0.76	1.11	0.91	0.76	1.07	Ref
Severe Mental Illness	0.90	0.66	1.24	0.82	0.65	1.02	0.87	0.72	1.06	Ref
Suicide Attempt	0.91	0.73	1.13	0.92	0.79	1.06	0.96	0.85	1.09	Ref
Criminality	1.01	0.94	1.09	1.00	0.95	1.05	0.99	0.95	1.04	Ref
Substance Use Problem	0.96	0.81	1.14	1.05	0.93	1.18	1.02	0.93	1.13	Ref
Failing Grades	0.98	0.90	1.08	0.90	0.85	0.96	0.94	0.89	0.98	Ref

Note: Number of differentially exposed sibling pairs included n= 569,802. Analyses adjusted for offspring sex, birth year, parity, and different father.

Table 4A. Hazard or odds ratios from long interpregnancy intervals predicting child and adult psychopathology

			Interpregnancy Interval (months)					
			24-35		36-71		72+	
Outcome variable and model			HR/OR	95% CI		HR/OR	95% CI	
ASD								
	Model 1	Ref	1.25	1.13	1.38	1.65	1.47	1.86
	Model 2	Ref	1.08	0.98	1.20	1.04	0.90	1.19
	Model 3	Ref	1.08	0.97	1.19	1.04	0.91	1.19
	Model 4 / Cousin-comparison	Ref	1.18	0.89	1.56	1.05	0.69	1.61
	Model 5 / Post-birth IPI	Ref	1.00	0.86	1.17	1.05	0.88	1.25
ADHD								
	Model 1	Ref	1.29	1.20	1.38	1.72	1.58	1.86
	Model 2	Ref	1.07	1.00	1.15	1.04	0.94	1.14
	Model 3	Ref	1.06	0.99	1.14	1.03	0.94	1.14
	Model 4 / Cousin-comparison	Ref	1.01	0.83	1.23	1.11	0.83	1.49
	Model 5 / Post-birth IPI	Ref	1.18	1.06	1.32	1.32	1.17	1.48
Severe Mental Illness								
	Model 1	Ref	1.16	1.06	1.23	1.55	1.37	1.76
	Model 2	Ref	1.06	0.97	1.16	1.12	0.97	1.29
	Model 3	Ref	1.06	0.97	1.16	1.13	0.97	1.16
	Model 4 / Cousin-comparison	Ref	1.14	0.90	1.43	0.88	0.61	1.29
	Model 5 / Post-birth IPI	Ref	0.93	0.81	1.05	1.10	0.95	1.26
Suicide Attempt								
	Model 1	Ref	1.14	1.07	1.21	1.22	1.11	1.34
	Model 2	Ref	1.04	0.97	1.11	0.89	0.80	0.99
	Model 3	Ref	1.03	0.97	1.11	0.90	0.81	1.00
	Model 4 / Cousin-comparison	Ref	1.01	0.87	1.18	1.02	0.81	1.29
	Model 5 / Post-birth IPI	Ref	0.92	0.83	1.01	1.15	1.04	1.27
Criminality								

Model 1	Ref	1.10	1.08	1.12	1.21	1.17	1.25
Model 2	Ref	1.04	1.01	1.06	0.98	0.95	1.01
Model 3	Ref	1.03	1.01	1.05	0.99	0.95	1.02
Model 4 / Cousin-comparison	Ref	1.03	0.98	1.08	0.97	0.90	1.04
Model 5 / Post-birth IPI	Ref	1.05	1.01	1.08	1.21	1.17	1.25
Substance Use Problem							
Model 1	Ref	1.16	1.10	1.22	1.43	1.33	1.53
Model 2	Ref	1.07	1.01	1.13	1.06	0.98	1.15
Model 3	Ref	1.06	1.00	1.12	1.07	0.99	1.16
Model 4 / Cousin-comparison	Ref	0.90	0.81	1.01	0.92	0.77	1.09
Model 5 / Post-birth IPI	Ref	1.03	0.96	1.12	1.25	1.15	1.36
Failing Grades							
Model 1	Ref	1.21	1.18	1.24	1.44	1.39	1.49
Model 2	Ref	1.10	1.08	1.13	1.08	1.04	1.13
Model 3	Ref	1.10	1.07	1.12	1.08	1.04	1.13
Model 4 / Cousin-comparison	Ref	1.00	0.90	1.11	0.95	0.86	1.06
Model 5 / Post-birth IPI	Ref	1.04	1.00	1.08	1.22	1.17	1.27

Note: A total of 216 641 (20.6%) of the sample had interpregnancy intervals of 36-71 months. A total of 74 503 (7.1%) of the sample had interpregnancy intervals of 72 or more months. Models were adjusted for the following measured covariates: *Model 1*: offspring sex, year of birth; *Model 2*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers; *Model 3*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers, maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness; *Model 4 / Cousin-comparison*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers, maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness; *Model 5 / Post-birth interpregnancy interval*: offspring sex, year of birth, maternal and paternal age, highest education, nationality, different fathers, maternal and paternal criminality, attempted suicide, substance misuse, and severe mental illness, first-born preterm birth, low birth weight, and small for gestational age. Model 5 Predicts the second-born's outcomes from the post-birth interpregnancy interval (interval between second-born and third-born) in a subsample of families with three children.