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Regular Article

Interpregnancy interval and the risk of oppositional defiant disorder in offspring

Berihun Assefa Dachew[1], Gavin Pereira[1,2,3], Gizachew Assefa Tessema[1,4], Gursimran Kaur Dhamrait[2,5] and Rosa Alati[1,6]

[1]School of Population Health, Curtin University, Perth, Western Australia, Australia, [2]Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia, [3]Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway, [4]School of Public Health, University of Adelaide, Adelaide, South Australia, Australia, [5]School of Population and Global Health, University of Western Australia, Perth, Western Australia, Australia and [6]Institute for Social Science Research, The University of Queensland, Brisbane, Queensland, Australia

Abstract

The study aimed to investigate the association between interpregnancy interval (IPI) and parent-reported oppositional defiant disorder (ODD) in offspring at 7 and 10 years of age. We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing population-based longitudinal study based in Bristol, United Kingdom (UK). Data included in the analysis consisted of more than 3200 mothers and their singleton children. The association between IPI and ODD was determined using a series of log-binomial regression analyses. We found that children of mothers with short IPI (<6 months) were 2.4 times as likely to have a diagnosis of ODD at 7 and 10 years compared to mothers with IPI of 18–23 months (RR = 2.45; 95%CI: 1.24–4.81 and RR = 2.40; 95% CI: 1.08–5.33), respectively. We found no evidence of associations between other IPI categories and risk of ODD in offspring in both age groups. Adjustment for a wide range of confounders, including maternal mental health, and comorbid ADHD did not alter the findings. This study suggests that the risk of ODD is higher among children born following short IPI (<6 months). Future large prospective studies are needed to elucidate the mechanisms explaining this association.

Keywords: ALSPAC; interpregnancy interval; offspring; oppositional defiant disorder

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Introduction

Oppositional defiant disorder (ODD) is a common child- and adolescent-onset disorder characterized by a frequent and persistent pattern of irritable and angry mood, argumentative and defiant behavior, aggression, and vindictiveness that lasts longer than 6 months (American Psychiatric Association, 2013). Children with ODD have deficits in academic, social, and occupational functioning and often develop other comorbid mental health disorders (American Psychiatric Association, 2013; Burke et al., 2014; Riley et al., 2016). The cause of ODD is unknown but likely involves a combination of genetic and environmental factors (Demontis et al., 2021; Ruisch et al., 2018). Therefore, it is important to identify early-life risk factors of ODD to better understand the etiology of the disorder and ultimately devise targeted early interventions for those affected.

Interpregnancy interval (IPI) is the duration between the birth of a previous child and the conception of the subsequent child (Ball et al., 2014). Existing observational studies have found both short and long IPIs are associated with a range of perinatal outcomes such as low birth weight, preterm birth, and small for gestational age (Conde-Agudelo et al., 2006; Mignini et al., 2016; Schummers et al., 2018; Shachar et al., 2016). For example, in a large retrospective birth cohort study, Shachar and colleagues (Shachar et al., 2016) found that women who conceive less than 6 months or within 6–11 months after giving birth have a 70% and 20% higher risk of preterm birth than women with an optimal IPI (18–23 months), respectively. The study also found 7% increased risk of preterm birth in women with longer IPI (>36 months) (Shachar et al., 2016). Recently studies have also suggested that both short and long IPIs are associated with an increased risk of neurodevelopmental disorders in offspring, including autism spectrum disorders (ASD) (Conde-Agudelo et al., 2016; Coo et al., 2015; Durkin et al., 2015; Elhakham et al., 2021; Gunnes et al., 2013; Zerbo et al., 2015) and attention deficit hyperactivity disorders (ADHD) (Cheslack-Postava et al., 2020; Class et al., 2018). In a population-based cohort study, Durkin et al. (2015) have reported a two-fold (OR = 2.16, 95% CI 1.32–3.53) increased risk of ASD in offspring of mothers with short IPI (<12 months). A more recent nested case–control Finnish study also reported a higher risk of ADHD among children born following short or long IPIs (Cheslack-Postava et al., 2020). Pregnancy-related physiological adaptation, maternal folate or nutritional depletion, adverse birth outcomes, sibling competition, parental stress, and neglectful parenting practices suggested as potential mechanisms for the associations between short or long IPIs and adverse behavioral

Corresponding author: Dr Berihun Dachew, email: berihun.dachew@curtin.edu.au
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and neurodevelopmental outcomes in offspring (Conde-Agudelo et al., 2012; Conde-Agudelo et al., 2016; Sanga et al., 2014; Thoma et al., 2019). Although an association between short and long IPIs and a higher risk of ASD and ADHD have been reported previously, we are not aware of any other study linking IPI with ODD. However, as ASD and ADHD are the most common comorbid conditions with ODD (Gadow et al., 2008; Riley et al., 2016), it is reasonable to postulate that short and long IPIs may increase the risk of ODD in offspring. Therefore, in this prospective general-population birth cohort study, we aimed to investigate the association between IPI and ODD in children at the age of 7 and 10 years, using the Avon Longitudinal Study of Parents and Children (ALSPAC) data, a birth cohort study with comprehensive data that can allow to account for a range of known confounders.

Methods

Data source and study participants

We used data from the ALSPAC, an ongoing population-based longitudinal birth cohort in Bristol, Avon, United Kingdom (UK). ALSPAC recruited 14,541 pregnant women residents in Avon, Southwest England, with expected delivery dates between April 1, 1991, and December 31, 1992 (Fraser et al., 2013; Golding et al., 2001). These pregnancies resulted in 14,062 live births, and 13,988 children were alive at 12 months of age. Children were invited to attend 9 assessment clinics, including face-to-face interviews and psychological and physical tests, from age 7 years onward. In the current study, women were included if they had two or more pregnancies that resulted in live births ($n = 7179$). The final analyses were conducted in children (singleton only) who had complete data on exposure, outcome and potential confounders ($n = 3582$ and 3290 at 7 and 10 years, respectively) (Figure 1). Further details regarding recruitment, study design, and generalizability have been previously reported (Boyd et al., 2013; Fraser et al., 2013), and the study website contains information of all the available data through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data). Ethical approval for the ALSPAC study was obtained from the ALSPAC Ethics and Law Committee as well as the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the ALSPAC Ethics and Law Committee's recommendations at the time. The details on the ethical approval, including the dates of approval and associated reference numbers, can be found at (http://www.bristol.ac.uk/alspac/researchers/research-ethics/).

Exposure

Women completed a questionnaire about their health, including the number and dates of previous pregnancies and outcomes, at the time of recruitment (approximately at 18 weeks gestation). IPI was defined as the length of time between the start of the index pregnancy (birth date minus gestational length) and the birth date of the preceding pregnancy and categorized as <6, 6–11, 12–17, 18–23, 24–35, ≥36 months, with 18–23 months used as the referent group. These intervals and the reference group are consistent with recommendations of existing studies and WHO recommendations (Ball et al., 2014; Marinovich et al., 2019; Tessema et al., 2021; Zhu et al., 1999).

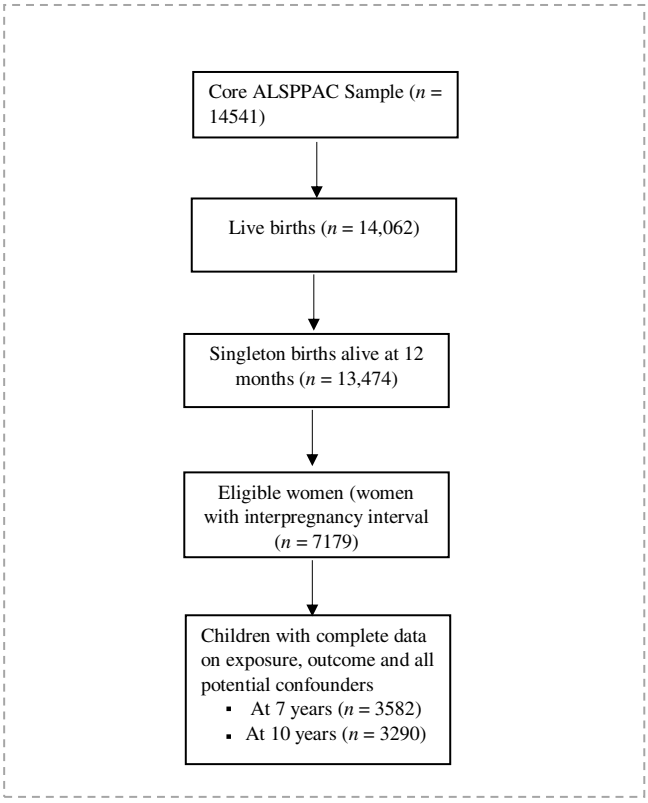

Figure 1. Children included in the analysis.

Outcome

Offspring ODD at the age of 7 and 10 years was assessed by using parental reports of the Development and Well-Being Assessment (DAWBA) (Goodman et al., 2011). The DAWBA is a validated diagnostic instrument combining structured and semi-structured questions that establish the presence of mental health disorders in children and adolescents (Goodman et al., 2011). The questions for each disorder closely follow the diagnostic criteria operationalized in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and the International Classification of Diseases, 10th revision (ICD-10) (Goodman et al., 2011). The responses were entered into a computer program that integrates the information and provides likely diagnoses where appropriate. These were then assessed by experienced clinical raters who decided whether to accept or overturn the computer diagnosis (or lack of it). Validation studies show substantial agreement between diagnoses generated by the DAWBA and clinician diagnoses, with κ coefficients of 0.84 (95%CI, 0.69–0.99) for any internalizing disorder, 0.89 (95%CI, 0.77–1.00) for any externalizing disorder, and 0.79 (95%CI, 0.39–1.00) for any other disorder (Aebi et al., 2012). The tool has been used in British nationwide surveys of child and adolescent mental health (Goodman et al., 2011).

Potential confounders

Potential confounders were selected on the basis of previous reports of their association with IPI and offspring neurodevelopmental and behavioral disorders. These include maternal and paternal age, maternal education, marital status, parity, pregnancy diabetes status, urinary tract infections (UTI) during pregnancy,

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hypertensive disorders during pregnancy, maternal smoking and alcohol use during pregnancy, maternal antenatal anxiety and depressive symptoms, and maternal folic acid and iron supplementations. Data on these potential confounders were obtained from obstetric records and questionnaires administered during pregnancy.

Statistical analysis

We conducted a series of log-binomial regression models to estimate risk ratios (RRs) and the corresponding 95% confidence intervals (CIs) for childhood ODD at 7 and 10 years, first without and then with adjustment for confounding variables. Model 1 was unadjusted. Model 2 adjusted for maternal and paternal age at birth, marital status, maternal education, parity, alcohol drinking during pregnancy, smoking during pregnancy, maternal antenatal depression and anxiety, UTI during pregnancy, pregnancy diabetes status, and hypertensive disorders during pregnancy. Maternal folic acid supplementation between subsequent pregnancies may be important to reduce the risk of adverse health outcomes associated with low folate status as a result of short IPIs (Nilsen et al., 2014). To account for this, we additionally adjusted Model 2 for maternal folic acid and iron supplementations during the current pregnancy (Model 3). In Model 4, we restricted our analysis to term and normal birth weight offspring. In a sensitivity analysis, we further adjusted the final model for ADHD, one of the most common comorbid conditions with ODD, occurring in 14% to 40% of children with the disorder (Riley et al., 2016). We also examined the association between IPI and persistent ODD in offspring by comparing offspring who had ODD diagnosis at both time points (i.e. 7 and 10 years) with those offspring with no ODD diagnosis.

A sample with complete data across all exposure, outcome, and confounding variables was used to investigate the impact of IPI on offspring ODD. We conducted sensitivity analyses using multivariate multiple imputations by chained equations to account for missing data. We used 50 cycles of regression switching and generated 50 imputed data sets. All covariates included in the regression model and additional auxiliary variables predictive of incomplete variables were included in the regression model and imputed, and the analyses were repeated. All statistical analyses were conducted using Stata 16 software (StataCorp 2019).

Results

Characteristics of mothers and children

Table 1 shows the characteristics of study participants included in the analysis. The mean (Standard deviation, SD) age of mothers was 29.7 (± 4.24) years and the majority were married (87.4%). About 16.6% of the mothers smoked tobacco and 15.1% consumed alcohol during their pregnancy. The prevalence of antenatal anxiety and depressive symptoms was 20.2% and 17.8%, respectively. Over 12% of children were born after a short IPI (<6 months). Around 3.7% ($n = 132$) of children aged 7 years and 3.2% ($n = 95$) of children aged 10 met the diagnostic criteria of ODD. Around 1.6% ($n = 46$) of children had an ODD diagnosis at both time points.

We compared participants with short IPIs with those who had longer IPIs on the key sociodemographic and clinical characteristics. Mothers of children with short IPI were more likely to be younger, married, educated, non-smokers, and had few children compared with mothers of children with longer IPIs (Table S1).

Table 1. Characteristics of study participants ($n = 3582$)

Characteristics	*n* (%)
Maternal age, mean (SD)	29.70 (4.24)
Paternal age, mean (SD)	32.29 (5.41)
Material status	
Never married	289 (8.07)
Widowed/divorced/Separated	163 (4.55)
Married	3130 (87.4)
Maternal education status[a]	
Certificate of Secondary Education	409 (11.42)
Vocational	336 (9.38)
O level	1323 (36.93)
A level	948 (26.47)
Degree	566 (15.80)
Parity	
1	2535 (70.22)
2	783 (21.86)
3	200 (5.58)
4+	64 (1.79)
Alcohol consumption during pregnancy	
Yes	542 (15.13)
No	3040 (84.87)
Smoking during pregnancy	
Smoker	596 (16.64)
Non-smoker	2986 (83.36)
Pregnancy diabetes status	
Yes	123 (3.43)
No	3459 (96.57)
Unitary tract infection during pregnancy	
Yes	171 (4.77)
No	3411 (95.23)
Hypertensive disorders during pregnancy	
Yes	438 (12.23)
No	3144 (87.77)
Antenatal anxiety	
Yes	725 (20.24)
No	2857 (79.76)
Antenatal depression	
Yes	615 (17.17)
No	2967 (82.83)
Folic acid supplementation	
Yes	332 (9.27)
No	3250 (90.73)
Iron supplementation	
Yes	723 (20.18)
No	2859 (79.82)

[a]O level (an examination taken and passed at 16 years of age) and A level (examinations taken and passed at 18 years of age upon leaving secondary school).

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Table 2. The association between IPI and offspring ODD at ages 7 and 10 years

		IPI categories					
		<6 months	6–11 months	12–17 months	18–23 months	24–35 months	>36 months
Offspring age	Models	RR (95% CI)					
7 Years ($n = 3582$)	Model 1	2.42 (1.25–4.67)	1.61 (0.81–3.21)	1.43 (0.73–2.81)	1 (Reference)	1.45 (0.74–2.83)	1.63 (0.86–3.11)
	Model 2	2.60 (1.33–5.05)	1.68 (0.85–3.35)	1.49 (0.76–2.93)	1 (Reference)	1.46 (0.75–2.85)	1.41 (0.73–2.73)
	Model 3	2.58 (1.33–5.02)	1.70 (0.85–3.38)	1.51 (0.77–2.97)	1 (Reference)	1.46 (0.75–2.84)	1.43 (0.74–2.76)
	Model 4	2.45 (1.24–4.81)	1.62 (0.81–3.25)	1.44 (0.73–2.85)	1 (Reference)	1.45 (0.74–2.82)	1.40 (0.72–2.72)
10 years ($n = 3290$)	Model 1	2.67 (1.23–5.80)	1.68 (0.74–3.80)	1.34 (0.58–3.06)	1 (Reference)	1.76 (0.81–3.82)	2.20 (1.04–4.65)
	Model 2	2.45 (1.11–5.42)	1.60 (0.70–3.62)	1.37 (0.60–3.13)	1 (Reference)	1.86 (0.86–4.04)	1.95 (0.91–4.20)
	Model 3	2.42 (1.10–5.35)	1.57 (0.69–3.56)	1.38 (0.60–3.15)	1 (Reference)	1.84 (0.85–4.00)	1.94 (0.90–4.18)
	Model 4	2.40 (1.08–5.33)	1.59 (0.70–3.61)	1.38 (0.60–3.15)	1 (Reference)	1.77 (0.81–3.86)	1.91 (0.88– 4.11)

Model 1 was unadjusted. Model 2 adjusted for maternal and paternal age at birth, marital status, maternal education, parity, alcohol drinking during pregnancy, smoking during pregnancy, maternal depression, maternal anxiety, and maternal urinary tract infection during pregnancy, pregnancy diabetes status, and hypertensive disorders during pregnancy. Model 3 further adjusted for folic acid and iron supplementation during pregnancy. Model 4 was Model 3, plus the sample was limited to term and normal birth weight offspring (this dropped the study sample to 3438 and 3170 at age 7 and 10 years, respectively).

We also compared characteristics of participants with and without ODD diagnosis and found that mothers of children with ODD were more likely to smoke during pregnancy and report anxiety and depressive symptoms than mothers of children without ODD. Similarly, the prevalence of ODD diagnosis varied substantially by sex (Table S2).

Table 2 shows univariable and multivariable associations between IPIs and offspring ODD at age 7 and 10 years. In the univariable analysis (Model 1), an IPI of <6 months was associated with higher odds of ODD in offspring. After adjusting for a wide range of confounding factors, including maternal antenatal depressive and anxiety symptoms (in Model 2), children after short IPI (< 6 months) were 2.6 and 2.5 times as likely to have a diagnosis of ODD at age 7 (RR = 2.60; 95%CI: 1.33–5.05) and 10 years (RR = 2.45; 95% CI: 1.11–5.42), respectively, compared with those born after IPIs of 18–23 months. Additional adjustment for maternal folic acid and iron supplementations during pregnancy did not alter the strengths of the associations (Model 3) [at 7 years; RR = 2.58; 95% CI: 1.33–5.02 and at 10 years; RR = 2.42; 95% CI: 1.10–5.35]. Restricting analyses to term and normal birthweight offspring (in Mode1 4) did not substantively change the results. Further adjustment for comorbid ADHD at each age group strengthened the association between short IPI (<6 months) and ODD in offspring but did not appreciably alter the findings (Table S3). We found no evidence of associations between other IPI categories and the risk of ODD except an elevated odds of ODD at age 10 years (RR = 2.20; 95% CI: 1.04–4.65) in offspring of mothers with longer IPI (>36 months). However, following adjustment, the observed association was not evident. We observed comparable results when we re-ran the models using the imputed data (Table S4).

Figure 2 shows the unadjusted and adjusted associations between IPIs and offspring ODD at age 7 and 10 years. Although the associations did not reach agreed standards for statistical significance, the pattern in the figure suggests the possibility of a U-shaped relation between IPI and ODD risk in offspring, with increased risk for both short and long intervals (Figure 2).

We also examined the association between IPI and persistent ODD (those who ODD diagnosis at both 7 and 10 years). After accounting for a range of confounders, we found that short IPI (<6 months) was associated with a 2.9 fold increased risk of persistent ODD (Table S5).

Discussion

In this population-based longitudinal birth cohort study, we found that short IPI <6 months was associated with an increased risk of ODD in offspring at ages 7 and 10. Adjustment for a wide range of known confounders and comorbid ADHD did not alter this association. Short IPIs of 6–11 months and 12–17 months were not associated with offspring ODD in both age groups. We also found no evidence of associations between longer IPIs (> 36 months) and the risk of ODD in offspring. The findings are somehow reassuring as only a very short IPI (< 6 months) was associated with an increased ODD risk in offspring.

Whilst, to our knowledge, no previous studies have examined the association between IPI and the risk of ODD in children, few studies have explored the impact of short and long IPIs on offspring neurodevelopmental and behavioral problems. Consistent with our findings, these studies have found a positive association between short IPI and adverse mental health outcomes in offspring (Cheslack-Postava et al., 2020; Class et al., 2018; Conde-Agudelo et al., 2016; Coo et al., 2015; Durkin et al., 2015; Gunnes et al., 2013; Zerbo et al., 2015). For example, using population-based Swedish data, Class et al. (2018) reported that an IPI of less than 6 months is associated with a 59% increased risk of ASD, although this study used 24–35 months as a reference category. A recent registry-based Finnish study also reported a 30% increased risk of ADHD among children born following a short (less than 6 months) IPI (Cheslack-Postava et al., 2020). Given ASD and ADHD are the most common comorbid conditions with ODD, occurring in up to 40% of children with the disorder (Gadow et al., 2008; Riley et al., 2016), the positive association between short IPI and ODD observed in this study may reflect that these disorders could have shared the same underlying mechanisms of associations with IPI.

While some of these studies also reported positive associations between other short IPI categories (6–11 months and/or 12–17 months) and adverse mental health outcomes in offspring (Class et al., 2018; Durkin et al., 2015; Gunnes et al., 2013; Zerbo et al., 2015), we found no evidence of associations at ages 7 and 10 years. Although our results are not directly comparable, the discrepancy in the results may be partly attributed to the difference in categories of intervals and/or reference categories used or might reflect true

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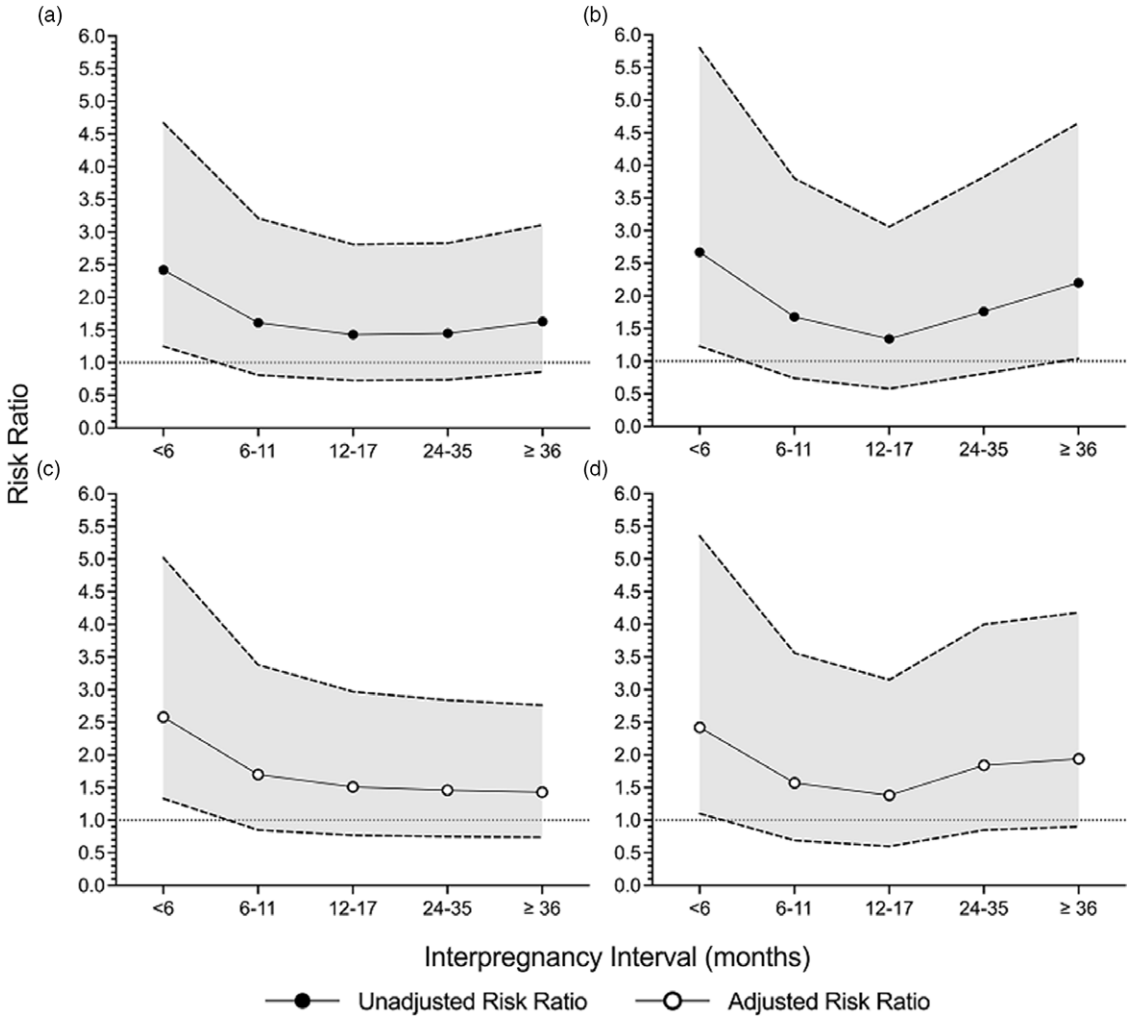

Figure 2. The association between IPI and the risk of ODD in children at age 7 (a and c) and 10 years (b and d) before and after adjustment for confounders.

differences between populations. For example, we used optimal IPI (18–23 months) (Marinovich et al., 2019; Zhu et al., 1999) as a reference group, while others used either long IPIs (>36 months) (Gunnes et al., 2013; Zerbo et al., 2015) or other reference categories (Class et al., 2018; Durkin et al., 2015).

We also found no evidence of associations between longer IPIs (> 36 months) and ODD risk in children. The association found in unadjusted analyses (at age 10 years) did not remain in the fully adjusted model. The available evidence on the relationship between long IPI and adverse mental health outcomes in offspring is limited and inconsistent (Conde-Agudelo et al., 2016). While some studies have reported offspring of mothers with long IPI are at increased risk for adverse mental health outcomes (Cheslack-Postava et al., 2020; Durkin et al., 2015; Zerbo et al., 2015), these links were not seen in other studies (Cheslack-Postava et al., 2011; Class et al., 2018; Sujan et al., 2019). In a large population-based cousin comparison design, Class et al. (2018) found no associations between long IPIs and a range of mental health and educational problems and suggested effect by familial confounding. Further research is needed to confirm the effect of long IPI on offspring mental health and behavioral problems.

There are several possible mechanisms by which short IPI could increase the risk of ODD in children. Maternal nutritional depletion as a result of short recovery time from the physiologic stresses of the preceding pregnancy is one of the plausible mechanisms. Folic acid is one of the most important nutrients for healthy fetal development, which plays an important role in neuronal development (Freedman et al., 2021; Pei et al., 2019). Folate deficiency affects DNA synthesis, repair, and methylation and can alter the expression of genes that regulate neurodevelopment (Brown & Susser 2008; Freedman et al., 2021). There is evidence that maternal serum and erythrocyte concentrations of folate decrease from mid-pregnancy onward and remain low during the early postpartum period (Brown & Susser 2008; Conde-Agudelo et al., 2016). Hence, women who become pregnant before folate restoration is complete are at increased risk of folate insufficiency (Doyle et al., 2001; Smits & Essed 2001), which could lead to altered neurodevelopment and partly responsible for the development of ODD in the early childhood period (Brown & Susser 2008; Freedman et al., 2021). While low maternal red blood cell folate in early pregnancy has been associated with higher risk of mental health outcomes in offspring (Roth et al., 2011; Roza et al., 2010; Schlotz et al., 2010), offspring of mothers who took folic acid supplements in the preconception, and/or early pregnancy period have been found to have reduced risk of neurodevelopmental and behavioral problems, including ASD, hyperactivity, inattention, and peer problems (Liu et al., 2021; Roza et al., 2010; Wang et al., 2017). In our study, adjustment for folic acid and iron

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supplementations prior to and/or during pregnancy did not change the observed association between short IPI (< 6 months) and offspring ODD. However, data on folic acid and iron supplementations were obtained by maternal self-reports, which are subject to report bias. Hence, more precise measures may be required to determine whether the risk associated with short IPI is modified by maternal use of folic acid and/or iron supplements.

An alternative pathway linking short IPI and an increased risk of ODD in offspring is through maternal inflammation. Short IPI may result in unresolved inflammation from the previous pregnancy (Getahun et al., 2010; Shachar & Lyell 2012), and elevation of maternal inflammatory biomarkers during pregnancy was found to be associated with a range of mental and neurodevelopmental disorders in offspring, including ODD (Brown et al., 2014; Han et al., 2021; Jones et al., 2021; Mac Giollabhui et al., 2019).

Another potential mechanism for the association between short IPI and ODD is through adverse birth outcomes, such as low birth weight and preterm births. Short IPI is associated with low birth weight and preterm births (Conde-Agudelo et al., 2006; Mignini et al., 2016; Schummers et al., 2018; Shachar et al., 2016), which are themselves risk factors for ODD and other neurodevelopmental and behavioral outcomes later in life (Johnson & Marlow 2011; Noordermeer et al., 2017; Scott et al., 2012). However, if these explain the possible mechanisms, we would expect reduced or no effects after restricting the analysis to term and normal birth weight offspring, but this was not the case (in Model 4), suggesting that low birth weight and preterm births did not explain the observed associations.

Unintended pregnancy (Sanga et al., 2014), sibling competition (Conde-Agudelo et al., 2012), parental stress, and neglectful parenting practices (Thoma et al., 2019) are other potential mechanisms linking short and the risk of ODD in offspring.

This study also has several important strengths. We used one of the most established longitudinal cohort studies in the world, the ALSPAC. The longitudinal design reduces the likelihood of recall bias. Offspring ODD was measured using the DAWBA, a valid and reliable diagnostic instrument that closely follow the diagnostic criteria operationalized DSM-IV and ICD-10. The availability of a wide range of confounders was an additional strength of our study.

Despite these strengths, our findings should be interpreted in light of the following limitations. As with all cohort studies, there was loss follow-up, which may introduce selection bias. Multiple imputations were used to address potential attrition bias; however, estimates from multiple imputations and complete case analyses were broadly comparable (Table S4). Our findings in this context are consistent with previous work in ALSPAC which found that selective drop-out did not bias the prediction of risk of behavioral disorders (Wolke et al., 2009). Consistent with this, a recent longitudinal study showed that loss to follow-up rarely affects estimates of associations (Saiepour et al., 2019). Taken together with this evidence, our multiple imputation analysis provides some confidence that attrition due to missing data is unlikely to have biased our results.

The further limitation is that the study was based on ALSPAC data in the UK; hence, our findings might not be generalizable to low- and middle-income countries where shorter IPIs are more prevalent. In addition, several of our confounding measures were based on maternal reports. Inaccurate maternal reports could have led to measurement error, which could have biased our findings.

While our data allowed us to adjust for a wide range of confounding factors, including maternal folic acid and iron supplementations, our findings may still be impacted by unmeasured genetic, epigenetic, and environmental confounders, which could bias the association between IPI and offspring ODD. However, adjustments for measured confounders barely change the estimates, suggesting our results were robust. Furthermore, we were unable to account for early pregnancy losses such as miscarriages and abortions, which could have led to overestimation of IPI in some women. It is also important to note that exclusion of women who had a history of miscarriage might have also biased our estimates for longer intervals toward the null, as an IPI of less than 6 months following a miscarriage was associated with lower risks of adverse birth outcomes (Kangatharan et al., 2017). In addition, we defined long IPI as greater than three years. We did not separately analyze long IPI categories due to small numbers; hence, the most extreme risk associated with the longest IPIs might not have been fully captured. Finally, although the prevalence of ODD in this study sample was consistent with the average prevalence estimate in the general population (3.3%) (American Psychiatric Association, 2013), the power of our analysis was limited by the relatively small number of children with ODD diagnosis at the age of 7 ($n = 132$) and 10 ($n = 104$) years in the study sample. Replication of our study in a larger sample would add weight to the current evidence.

Our study showed that short IPI (<6 months) was associated with an increased risk of ODD in offspring. This association was not explained by low birth weight, preterm birth, and a wide range of measured confounders. Since IPI is a potentially modifiable risk factor, our findings have important clinical and public health implications.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S095457942200013X

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Conflicts of interest. None.

References

Aebi, M., Kuhn, C., Metzke, C. W., Stringaris, A., Goodman, R., & Steinhausen, H.-C. (2012). The use of the development and well-being assessment (DAWBA) in clinical practice: A randomized trial. *European Child & Adolescent Psychiatry*, *21*(10), 559–567. https://doi.org/10.1007/s00787-012-0293-6

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

Ball, S. J., Pereira, G., Jacoby, P., de Klerk, N., & Stanley, F. J. (2014). Re-evaluation of link between interpregnancy interval and adverse birth outcomes: Retrospective cohort study matching two intervals per mother. *The British Medical Journal*, *349*, g4333. https://doi.org/10.1136/bmj.g4333

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J. . . . **Davey Smith, G.** (2013). Cohort Profile: The 'children of the 90s'–

the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology*, *42*(1), 111–127. https://doi.org/10.1093/ije/dys064

Brown, A. S., Sourander, A., Hinkka-Yli-Salomäki, S., McKeague, I. W., Sundvall, J., & Surcel, H. M. (2014). Elevated maternal C-reactive protein and autism in a national birth cohort. *Mol Psychiatry*, *19*(2), 259–264. https://doi.org/10.1038/mp.2012.197

Brown, A. S., & Susser, E. S. (2008). Prenatal nutritional deficiency and risk of adult schizophrenia. *Schizophr Bull*, *34*(6), 1054–1063. https://doi.org/10.1093/schbul/sbn096

Burke, J. D., Rowe, R., & Boylan, K. (2014). Functional outcomes of child and adolescent oppositional defiant disorder symptoms in young adult men. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *55*(3), 264–272. https://doi.org/10.1111/jcpp.12150

Cheslack-Postava, K., Liu, K., & Bearman, P. S. (2011). Closely spaced pregnancies are associated with increased odds of autism in California sibling births. *Pediatrics*, *127*(2), 246–253. https://doi.org/10.1542/peds.2010-2371

Cheslack-Postava, K., Sourander, A., Suominen, A., Jokiranta-Olkoniemi, E., McKeague, I. W., & Brown, A. S. (2020). Increased risk of ADHD at short and long interpregnancy intervals in a national birth cohort. *Paediatric and Perinatal Epidemiology*, https://doi.org/10.1111/ppe.12657

Class, Q. A., Rickert, M. E., Larsson, H., Oberg, A. S., Sujan, A. C., Almqvist, C. . . . **D'Onofrio, B. M.** (2018). Outcome-dependent associations between short interpregnancy interval and offspring psychological and educational problems: A population-based quasi-experimental study. *International Journal of Epidemiology*, *47*(4), 1159–1168. https://doi.org/10.1093/ije/dyy042

Conde-Agudelo, A., Rosas-Bermudez, A., Castaño, F., & Norton, M. H. (2012). Effects of birth spacing on maternal, perinatal, infant, and child health: A systematic review of causal mechanisms. *Studies in Family Planning*, *43*(2), 93–114. https://doi.org/10.1111/j.1728-4465.2012.00308.x

Conde-Agudelo, A., Rosas-Bermúdez, A., & Kafury-Goeta, A. C. (2006). Birth spacing and risk of adverse perinatal outcomes: A meta-analysis. *Journal of the American Medical Association*, *295*(15), 1809–1823. https://doi.org/10.1001/jama.295.15.1809

Conde-Agudelo, A., Rosas-Bermudez, A., & Norton, M. H. (2016). Birth spacing and risk of autism and other neurodevelopmental disabilities: A systematic review. *Pediatrics*, *137*(5). https://doi.org/10.1542/peds.2015-3482

Coo, H., Ouellette-Kuntz, H., Lam, Y. M., Brownell, M., Flavin, M. P., & Roos, L. L. (2015). The association between the interpregnancy interval and autism spectrum disorder in a Canadian cohort. *Canadian Journal of Public Health*, *106*(2), e36–42. https://doi.org/10.17269/cjph.106.4667

Demontis, D., Walters, R. K., Rajagopal, V. M., Waldman, I. D., Grove, J., Als, T. D. . . . **Børglum, A. D.** (2021). Risk variants and polygenic architecture of disruptive behavior disorders in the context of attention-deficit/hyperactivity disorder. *Nature Communications*, *12*(1), 576. https://doi.org/10.1038/s41467-020-20443-2

Doyle, W., Srivastava, A., Crawford, M. A., Bhatti, R., Brooke, Z., & Costeloe, K. L. (2001). Inter-pregnancy folate and iron status of women in an inner-city population. *British Journal of Nutrition*, *86*(1), 81–87. https://doi.org/10.1079/bjn2001376

Durkin, M. S., DuBois, L. A., & Maenner, M. J. (2015). Inter-pregnancy intervals and the risk of autism spectrum disorder: Results of a population-based study. *Journal of Autism and Developmental Disorders*, *45*(7), 2056–2066. https://doi.org/10.1007/s10803-015-2368-y

Elhakham, D., Wainstock, T., Sheiner, E., Sergienko, R., & Pariente, G. (2021). Inter-pregnancy interval and long-term neurological morbidity of the offspring. *Archives of Gynecology and Obstetrics*, *303*(3), 703–708. https://doi.org/10.1007/s00404-020-05788-9

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G. . . . **Lawlor, D. A.** (2013). Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology*, *42*(1), 97–110. https://doi.org/10.1093/ije/dys066

Freedman, R., Hunter, S. K., Law, A. J., Clark, A. M., Roberts, A., & Hoffman, M. C. (2021). Choline, folic acid, Vitamin D, and fetal brain development in the psychosis spectrum. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2021.03.008

Gadow, K. D., Devincent, C. J., & Drabick, D. A. (2008). Oppositional defiant disorder as a clinical phenotype in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *38*(7), 1302–1310. https://doi.org/10.1007/s10803-007-0516-8

Getahun, D., Strickland, D., Ananth, C. V., Fassett, M. J., Sacks, D. A., Kirby, R. S., & Jacobsen, S. J. (2010). Recurrence of preterm premature rupture of membranes in relation to interval between pregnancies. *American Journal of Obstetrics & Gynecology*, *202*(6), 570.e1–570.e6. https://doi.org/10.1016/j.ajog.2009.12.010

Golding, J., Pembrey, M., & Jones, R. (2001). ALSPAC–The Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatric and Perinatal Epidemiology*, *15*(1), 74–87. https://doi.org/10.1046/j.1365-3016.2001.00325.x

Goodman, A., Heiervang, E., Collishaw, S., & Goodman, R. (2011). The 'DAWBA bands' as an ordered-categorical measure of child mental health: Description and validation in British and Norwegian samples. *Social Psychiatry and Psychiatric Epidemiology*, *46*(6), 521–532. https://doi.org/10.1007/s00127-010-0219-x

Gunnes, N., Suren, P., Bresnahan, M., Hornig, M., Lie, K. K., Lipkin, W. I. . . . **Stoltenberg, C.** (2013). Interpregnancy interval and risk of autistic disorder. *Epidemiology*, *24*(6), 906–912. https://doi.org/10.1097/01.ede.0000434435.52506.f5

Han, V. X., Patel, S., Jones, H. F., Nielsen, T. C., Mohammad, S. S., Hofer, M. J. . . . **Dale, R. C.** (2021). Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: A systematic review. *Translational Psychiatry*, *11*(1), 71. https://doi.org/10.1038/s41398-021-01198-w

Johnson, S., & Marlow, N. (2011). Preterm birth and childhood psychiatric disorders. *Pediatric Research*, *69*(8), 11–18. https://doi.org/10.1203/PDR.0b013e318212faa0

Jones, H. F., Han, V. X., Patel, S., Gloss, B. S., Soler, N., Ho, A. . . . **Dale, R. C.** (2021). Maternal autoimmunity and inflammation are associated with childhood tics and obsessive-compulsive disorder: Transcriptomic data show common enriched innate immune pathways. *Brain, Behavior, and Immunity*, *94*, 308–317. https://doi.org/https://doi.org/10.1016/j.bbi.2020.12.035

Kangatharan, C., Labram, S., & Bhattacharya, S. (2017). Interpregnancy interval following miscarriage and adverse pregnancy outcomes: Systematic review and meta-analysis. *Human Reproduction Update*, *23*(2), 221–231. https://doi.org/10.1093/humupd/dmw043

Liu, X., Zou, M., Sun, C., Wu, L., & Chen, W. X. (2021). Prenatal folic acid supplements and offspring's autism spectrum disorder: A meta-analysis and meta-regression. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-021-04951-8

Mac Giollabhui, N., Breen, E. C., Murphy, S. K., Maxwell, S. D., Cohn, B. A., Krigbaum, N. Y. . . . **Ellman, L. M.** (2019). Maternal inflammation during pregnancy and offspring psychiatric symptoms in childhood: Timing and sex matter. *Journal of Psychiatric Research*, *111*, 96–103. https://doi.org/10.1016/j.jpsychires.2019.01.009

Marinovich, M. L., Regan, A. K., Gissler, M., Magnus, M. C., Håberg, S. E., Padula, A. M. . . . **Pereira, G. F.** (2019). Developing evidence-based recommendations for optimal interpregnancy intervals in high-income countries: Protocol for an international cohort study. *BMJ Open*, *9*(1), e027941. https://doi.org/10.1136/bmjopen-2018-027941

Mignini, L. E., Carroli, G., Betran, A. P., Fescina, R., Cuesta, C., Campodonico, L. . . . **Khan, K. S.** (2016). Interpregnancy interval and perinatal outcomes across Latin America from 1990 to 2009: A large multi-country study. *BJOG: An International Journal of Obstetrics & Gynaecology*, *123*(5), 730–737. https://doi.org/10.1111/1471-0528.13625

Nilsen, R. M., Mastroiacovo, P., Gunnes, N., Alsaker, E. R., Bjørke-Monsen, A. L., Eussen, S. J. . . . **Vollset, S. E.** (2014). Folic acid supplementation and interpregnancy interval. *Paediatric and Perinatal Epidemiology*, *28*(3), 270–274. https://doi.org/10.1111/ppe.12111

Noordermeer, S. D. S., Luman, M., Weeda, W. D., Buitelaar, J. K., Richards, J. S., Hartman, C. A. . . . **Oosterlaan, J.** (2017). Risk factors for comorbid oppositional defiant disorder in attention-deficit/hyperactivity disorder. *European Child & Adolescent Psychiatry*, *26*(10), 1155–1164. https://doi.org/10.1007/s00787-017-0972-4

Pei, L., Wu, J., Li, J., Mi, X., Zhang, X., Li, Z., & Zhang, Y. (2019). Effect of periconceptional folic acid supplementation on the risk of neural tube defects associated with a previous spontaneous abortion or maternal first-trimester fever. *Human Reproduction*, *34*(8), 1587–1594. https://doi.org/10.1093/humrep/dez112

Riley, M., Ahmed, S., & Locke, A. (2016). Common questions about oppositional defiant disorder. *American Family Physician*, *93*(7), 586–591. https://www.aafp.org/afp/2016/0401/afp20160401p586.pdf

Roth, C., Magnus, P., Schjølberg, S., Stoltenberg, C., Surén, P., McKeague, I. W. . . . **Susser, E.** (2011). Folic acid supplements in pregnancy and severe language delay in children. *Journal of the American Medical Association*, *306*(14), 1566–1573. https://doi.org/10.1001/jama.2011.1433

Roza, S. J., van Batenburg-Eddes, T., Steegers, E. A., Jaddoe, V. W., Mackenbach, J. P., Hofman, A. . . . **Tiemeier, H.** (2010). Maternal folic acid supplement use in early pregnancy and child behavioural problems: The Generation R Study. *British Journal of Nutrition*, *103*(3), 445–452. https://doi.org/10.1017/s0007114509991954

Ruisch, I. H., Buitelaar, J. K., Glennon, J. C., Hoekstra, P. J., & Dietrich, A. (2018). Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the Avon Longitudinal Study of Parents and Children. *Journal of psychiatric research*, *101*, 63–71. https://doi.org/10.1016/j.jpsychires.2018.02.020

Saiepour, N., Najman, J. M., Ware, R., Baker, P., Clavarino, A. M., & Williams, G. M. (2019). Does attrition affect estimates of association: A longitudinal study. *Journal of Psychiatric Research*, *110*, 127–142. https://doi.org/https://doi.org/10.1016/j.jpsychires.2018.12.022

Sanga, K., Mola, G., Wattimena, J., Justesen, A., & Black, K. I. (2014). Unintended pregnancy amongst women attending antenatal clinics at the Port Moresby General Hospital. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *54*(4), 360–365. https://doi.org/10.1111/ajo.12219

Schlotz, W., Jones, A., Phillips, D. I., Gale, C. R., Robinson, S. M., & Godfrey, K. M. (2010). Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *Journal of Child Psychology and Psychiatry*, *51*(5), 594–602. https://doi.org/10.1111/j.1469-7610.2009.02182.x

Schummers, L., Hutcheon, J. A., Hernandez-Diaz, S., Williams, P. L., Hacker, M. R., VanderWeele, T. J., & Norman, W. V. (2018). Association of short interpregnancy interval with pregnancy outcomes according to maternal age. *JAMA Internal Medicine*, *178*(12), 1661–1670. https://doi.org/10.1001/jamainternmed.2018.4696

Scott, M. N., Taylor, H. G., Fristad, M. A., Klein, N., Espy, K. A., Minich, N., & Hack, M. (2012). Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. *Journal of Developmental and Behavioral Pediatrics*, *33*(3), 202–213. https://doi.org/10.1097/DBP.0b013e3182475287

Shachar, B. Z., & Lyell, D. J. (2012). Interpregnancy interval and obstetrical complications. *Obstetrical and Gynecological Survey*, *67*(9), 584–596. https://doi.org/10.1097/OGX.0b013e31826b2c3e

Shachar, B. Z., Mayo, J. A., Lyell, D. J., Baer, R. J., Jeliffe-Pawlowski, L. L., Stevenson, D. K., & Shaw, G. M. (2016). Interpregnancy interval after live birth or pregnancy termination and estimated risk of preterm birth: A retrospective cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology*, *123*(12), 2009–2017. https://doi.org/10.1111/1471-0528.14165

Smits, L. J., & Essed, G. G. (2001). Short interpregnancy intervals and unfavourable pregnancy outcome: Role of folate depletion. *Lancet*, *358*(9298), 2074–2077. https://doi.org/10.1016/s0140-6736(01)07105-7

StataCorp (2019). *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

Sujan, A. C., Class, Q. A., Rickert, M. E., Van Hulle, C., & D'Onofrio, B. M. (2019). Risk factors and child outcomes associated with short and long interpregnancy intervals. *Early Child Development and Care*, *191*, 2281–2292. https://doi.org/10.1080/03004430.2019.1703111

Tessema, G. A., Marinovich, M. L., Håberg, S. E., Gissler, M., Mayo, J. A., Nassar, N. . . . **Pereira, G.** (2021). Interpregnancy intervals and adverse birth outcomes in high-income countries: An international cohort study. *PLoS One*, *16*(7), e0255000. https://doi.org/10.1371/journal.pone.0255000

Thoma, M. E., Rossen, L. M., De Silva, D. A., Warner, M., Simon, A. E., Moskosky, S., & Ahrens, K. A. (2019). Beyond birth outcomes: Interpregnancy interval and injury-related infant mortality. *Paediatric and Perinatal Epidemiology*, *33*(5), 360–370. https://doi.org/10.1111/ppe.12575

Wang, M., Li, K., Zhao, D., & Li, L. (2017). The association between maternal use of folic acid supplements during pregnancy and risk of autism spectrum disorders in children: A meta-analysis. *Molecular Autism*, *8*, 51. https://doi.org/10.1186/s13229-017-0170-8

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *British Journal of Psychiatry*, *195*(3), 249–256. https://doi.org/10.1192/bjp.bp.108.053751

Zerbo, O., Yoshida, C., Gunderson, E. P., Dorward, K., & Croen, L. A. (2015). Interpregnancy interval and risk of autism spectrum disorders. *Pediatrics*, *136*(4), 651–657. https://doi.org/10.1542/peds.2015-1099

Zhu, B. P., Rolfs, R. T., Nangle, B. E., & Horan, J. M. (1999). Effect of the interval between pregnancies on perinatal outcomes. *The New England Journal of Medicine*, *340*(8), 589–594. https://doi.org/10.1056/nejm199902253400801