Optimal interpregnancy interval in Autism Spectrum Disorder: a multi-national study of a modifiable risk factor

Short title: Pregnancy intervals and autism spectrum disorder

Gavin Pereira,[1, 2, 3] Richard W. Francis,[2] Mika Gissler,[4,5,6] Stefan N. Hansen,[7] Arad Kodesh,[8,9] Helen Leonard,[2,10] Stephen Z. Levine,[8] Vera R. Mitter,[3] Eric T. Parner,[7] Annette K. Regan,[1,11,12] Abraham Reichenberg,[13] Sven Sandin,[14,15,16] Auli Suominen,[5] Diana Schendel[17,18,19,20]

1. Curtin School of Population Health, Curtin University, WA, Australia
2. enAble Institute, Curtin University, WA, Australia
3. Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
4. THL Finnish Institute for Health and Welfare, Information Services Department, Helsinki, Finland
5. Research Centre for Child Psychiatry, University of Turku, Turku, Finland
6. Department of Neurobiology, Care Sciences and Society & Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden
7. Research Unit for Biostatistics, Department of Public Health, Aarhus University, Aarhus, Denmark
8. Department of Community Mental Health, University of Haifa, Haifa 31905, Israel
9. Meuhedet Health Services, Mental Health, Tel Aviv, Israel
10. University of Western Australia, Perth, Western Australia
11. School of Nursing and Health Professions, University of San Francisco, San Francisco CA, United States
12. Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA, United States
13. Departments of Psychiatry and Environmental Medicine and Public Health; Mindich Child Health and Development Institute; Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, NY, USA
14. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
15. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA
16. Seaver Autism Center for Research and Treatment at Mount Sinai, New York, USA
17. National Centre for Register-based Research, Department of Economics and Business, Aarhus University, Aarhus, Denmark
18. Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark
19. Research Unit for Epidemiology; Department of Public Health, Aarhus University, Aarhus, Denmark
20. AJ Drexel Autism Institute, Drexel University, Philadelphia, USA

Correspondence to: Professor Gavin Pereira
School of Public Health
Curtin University
Perth, WA 6102, Australia
Gavin.f.pereira@curtin.edu.au
+61 8 9266 3940

Acknowledgements

The authors wish to thank the data custodians of the registries from Denmark, Finland and Sweden that were used in this study. This project was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (HD073978), National Institute of Environmental Health Sciences, and National Institute of Neurological Disorders. GP was supported with funding from the Australian National Health and Medical Research Council (NHMRC) project and investigator grants (#1099655 and #1173991) and the Research Council of Norway through its Centres of Excellence funding scheme (#262700) and institutional support for the WA Health and Artificial Intelligence Consortium. HL was supported by an

NHMRC Senior Research Fellowship (#1117105). VRM was supported by a Swiss National Science Foundation Early Postdoc Mobility Grant (#P2BEP3 191798).

ABSTRACT

It is biologically plausible that risk of autism spectrum disorder (ASD) is elevated by both short and long interpregnancy intervals (IPI). We conducted a retrospective cohort study of singleton, non-nulliparous live births, 1998-2007 in Denmark, Finland, and Sweden (N = 925,523 births). Optimal IPI was defined as the IPI at which minimum risk was observed. Generalised additive models were used to estimate relative risks (RR) of ASD and 95% Confidence Intervals (CI). Population impact fractions (PIF) for ASD were estimated under scenarios for shifts in the IPI distribution.We observed that the association between ASD (N=9,302) and IPI was U-shaped for all countries. ASD risk was lowest (optimal IPI) at 35 months for all countries combined, and at 30, 33 and 39 months in Denmark, Finland and Sweden, respectively. Fully adjusted RRs at IPIs of 6, 12 and 60 months were 1.41 (95% CI: 1.08, 1.85), 1.26 (95% CI: 1.02, 1.56) and 1.24 (95% CI: 0.98, 1.58) compared to an IPI of 35 months. Under the most conservative scenario PIFs ranged from 5% (95% CI: 1% to 8%) in Denmark to 9% (95% CI: 6% to 12%) in Sweden. The minimum ASD risk followed IPIs of 30-39 months across three countries. These results reflect both direct IPI effects and other, closely related social and biological pathways. If our results reflect biologically causal effects, increasing optimal IPIs and reducing their indications, such as unintended pregnancy and delayed age at first pregnancy has the potential to prevent a salient proportion of ASD cases.

MeSH keywords. Autism Spectrum Disorder, Birth Intervals, Family Planning Services, Longitudinal Studies

Lay summary. Waiting 35 months to conceive again after giving birth resulted in the least risk of autism. Shorter and longer intervals resulted in risks that were up to 50% and 85% higher, respectively. About 5% to 9% of autism cases might be avoided by optimizing birth spacing.

INTRODUCTION

Previous studies have reported elevated risk of autism spectrum disorder (ASD) ASD in offspring following both short and long interpregnancy intervals (IPI).(Cheslack-Postava, Liu, & Bearman, 2011; Dodds et al., 2011; Durkin, DuBois, & Maenner, 2015; Gunnes et al., 2013) Although mechanisms are not well-understood, elevated risk is biologically plausible due to inadequate recovery from micronutrient depletion or time to resolve inflammation after short intervals, or due to physiological regression to a primigravid state from loss of vascular adaptation after long intervals.(Keely Cheslack-Postava et al., 2014; Conde-Agudelo, Rosas-Bermudez, Castaño, & Norton, 2012)

A meta-analysis of five studies and almost 5,000 ASD cases from the United States, Norway, and Canada concluded that intervals shorter than 12 months are associated with almost two times greater odds of ASD compared to intervals longer than 36 months.(Conde-Agudelo, Rosas-Bermudez, & Norton, 2016) However, the authors also reported significant variation in results across studies. More recent findings from an extensive study of more than six thousand ASD cases suggested that previous observational associations might be explained by genetic or shared environmental confounding; the large variation in results observed in the prior meta-analysis might be partly explained by uncontrolled familial confounding.(Class et al., 2018) Moreover, meta-analyses are limited by differences in the methodology employed by each of the contributing studies and are prone to ecological fallacy whereby simple aggregation of results across sites or countries into a single pooled effect is erroneously assumed to hold for individuals.(Thomas, Radji, & Benedetti, 2014) To our knowledge, no large-scale, individual-level study of IPI and ASD has been conducted across multiple countries. It is also uncertain if ASD – IPI associations are robust after control for familial predisposition, and if so, what is the optimal IPI at which risk of ASD can be minimised.(Riley, Lambert, & Abo-Zaid, 2010)

The current study aimed to quantify the association between IPI and ASD in several high-income countries with universal health care and well-established parental leave systems, using a common protocol and controlling for family-level factors, to identify the optimal IPI at which risk might be minimised.

MATERIALS AND METHODS

Design and Study Population

This was a retrospective cohort study of all registered non-nulliparous singleton live births during the period 1998 - 2007 in three high-income countries (Denmark, Finland, and Sweden) with comprehensive follow-up for ASD until 31 December 2012. Each index birth in the cohort was linked to the mother and her previous livebirths.

Data Source

The study data were derived from *MINERvA*, an international collaborative network investigating familial and environmental contributions to risk for ASD. Details of the *MINERvA* cohort have been published previously.(Hansen et al., 2019; Sandin et al., 2016) Briefly, MINERvA data are derived from population-based registries maintained in each participating country which include linkable, prospectively collected, individual-level information on births and birth outcomes, family linkages, deaths, medical contacts and health outcomes including psychiatric disorders.(Hansen et al., 2019)

Assessment of Autism Spectrum Disorder

ASD diagnoses were identified for members of the study cohort and older siblings and examined in this study as a binary indicator ASD. For all countries, ASD was identified from health registries, including both inpatient and outpatient records.(Schendel et al., 2013) The same diagnostic systems were used across sites during the study period and the diagnostic codes for ASD were harmonized, using the following diagnostic codes: ICD-8 (299.00/01/02/03), ICD-9 (299.0/8/9), ICD-10 (F84.0/1/5/8/9).

Derivation of Interpregnancy Interval

Interpregnancy interval was derived as the time (months) between the date of the previous live birth and conception of the cohort pregnancy. Further information on the derivation of IPI and data availability for each country can be found in the Supplementary Material. We summarised IPI according to WHO categories(Marston, 2006) and treated IPI as a continuous variable for analyses.

Covariates

Covariates included parity at birth of the cohort child, categorised as 1, 2 and 3 corresponding to the 2nd 3rd and 4th livebirth respectively (and higher parity births were excluded, see Exclusions). Other covariates included maternal and paternal ages at birth of the cohort child, an indicator for at least one parent born outside the cohort country, an indicator for maternal smoking during pregnancy of the cohort child, parental history of psychiatric diagnoses, year of birth of the cohort child, and follow-up time. Follow-up time was derived as the time from birth to the end of the study period. Parental psychiatric history at birth of the cohort child was a binary indicator for psychiatric conditions (ICD-8: 290-315.9, excluding 302; ICD-9: 648.4, 290-319, excluding 302; ICD-10: F00-F99) for the mother and father diagnosed at any time prior to birth of the cohort child. Maternal mean IPI was derived as the arithmetic mean of IPIs for all cohort children to the same mother. Covariates were selected based on both availability within the MINERvA cohort and their role on the hypothesized causal pathway, described with a directed acyclic graph (Supplementary Material, Figure S1). Covariates were defined at the birth of the cohort child (rather than at the birth preceding the IPI) because we are interested in the spacing effect that is independent of aging and other covariates that continue to change after the start of the IPI.

Exclusions

From a starting population of 2,202,689 live births, we excluded sequentially births with missing parity (N=40,082; 1.82%) and first births (parity 0; N=931,271; 43.06%) (Supplementary Material, Table S1). We then excluded births for which IPI could not be calculated due to lack of information on the previous birth (N=232,928; 18.92%), the majority of which were from Denmark due to lack of birth date data for older siblings born prior to the study period. Next we excluded multiple gestation births (N=25,124; 2.52%). Of the births that followed a confirmed ASD diagnosis of the immediate previous birth (N=10,301) we excluded those whose conception dates were after the ASD diagnosis (N=248; 0.03% of the total sample) because parents may intentionally delay subsequent pregnancy after their child's ASD diagnosis. Grand multipara births, defined as parity of four or more (N=47,513; 4.88%), were excluded because they would have otherwise contributed a disproportionately large number of higher-risk births with IPIs to risk estimates. These

exclusions left a study population consisting of 925,523 births (Denmark, N=198,693; Finland, N=295,389; and Sweden, N=431,441) of which 9,302 births had a diagnosis of ASD after the IPI (Denmark, N=2,047; Finland, N=1,707; and Sweden, N=5,548).

Imputation of Missing Covariates

Due to the low proportion of missing data, only paternal age (N=6,680; 0.72% missing) and maternal smoking (N=39,842; 4.30% missing) were imputed by stochastic regression imputation using Generalised Additive Models with country, parity, an indicator for at least one parent born outside the cohort country, parental history of psychiatric diagnoses, and thin plate spline functions of year of birth, follow-up time, and maternal age as predictors. Smoothing parameters were selected by restricted maximum likelihood estimation.

Statistical Analyses

Log-binomial Generalised Additive Models (GAM) were used to estimate risk of ASD associated with IPI.(Wood, 2017) A GAM is a generalised linear model of the association between an outcome (ASD) and exposure (IPI) with non-parametric functions that allow the shape of the association to be non-linear and completely determined from the observed data. Random intercepts were used to account for births to the same mother. Linear temporal trends in ASD and follow-up time were controlled by adjustment. Nonlinear associations with IPI were modelled with penalised thin plate regression splines that were allowed to vary between country. We reported results for sequential models, first with no adjustment, next we added adjustment for covariates, and finally we further adjusted for a non-linear spline function of maternal mean IPI as a proxy for unmeasured confounders shared in the family that are associated with both IPI and elevated risk of ASD.(Begg & Parides, 2003) We calculated Relative Risk (RR) and 95% Confidence Intervals (CI) for each whole month of IPI from 3 months to 120 months with the IPI corresponding to the minimum RR along this IPI range defined as the optimal IPI and used as the reference category. All analyses were conducted in R version 3.5.2 (*mgcv* v1.8).(Wood, 2011) Further details on the statistical analysis can be found in the Supplementary Material.

Potential Impact Fractions

We calculated the percentage of ASD cases that were potentially attributable to non-optimal IPI (population attributable fraction , PAF) and the percentage of ASD cases potentially prevented if the IPI distribution changed (potential impact fraction, PIF). The PIFs were calculated under various scenarios: 100%, 90% or 75% of mothers adopt the observed optimal IPIs; and mothers with unintended (classified as "unwanted" and/or "mistimed") pregnancies, do not adopt the observed optimal IPIs.(Ahrens et al., 2018) We calculated 95% centile intervals (CI) for PIFs by simulation, using the corrected centile method applied to the lower (2.5^{th}) and the upper (97.5^{th}) centiles of the RR distribution. Further information on methods for the PIFs and CIs is provided in the Supplementary Material.

Sensitivity Analyses

We conducted sensitivity analyses to assess the potential influence of several sources of bias. Firstly, to assess the influence of bias from country-level differences in parity distributions we repeated analyses after restriction of the cohort to births at parity 1. Secondly, bias can potentially result from differences between countries in the date range of births before the study period and from missingness that varies over time. Notably, IPI was derived using only births during the study period for Denmark (Supplementary Material, Derivation of IPI) and there were relatively more IPIs missing for Sweden (Supplementary Material, Table S1), which decreased during the study period. Consequently, we repeated analyses after restriction of the cohort to births from 2003, thereby reducing the influence of such temporal bias and allowing for at least five years of follow-up in all countries. Next, we conducted two separate sensitivity analyses after restriction of the cohort to births that did not follow a confirmed ASD diagnosis in the immediate previous birth, and after adjustment for confirmed ASD diagnosis in the immediate previous birth. We conducted a further sensitivity analysis that included additional adjustment for nonlinear spline functions of maternal and paternal education (Finland and Sweden) and marital status (Denmark and Finland). Finally, we investigated the specificity of our results within the ASD spectrum after repeating analyses after restricting the ASD outcome to the autistic disorder subtype (ICD-10 F84.0). We did not produce cluster-adjusted results for sensitivity analyses that restricted the study population because restriction reduces the sample of mothers with more than one IPI.

Ethical Approval

The study was conducted in compliance with the Declaration of Helsinki and approved by the Human Research Ethics Committees and Institutional Review Boards at the respective sites in Denmark (Danish Data Protection Agency: 2013-41-2462), Finland (Hospital District of Southwest Finland ETMK: 93/1802/2014) and Sweden (Etikprövningsmyndigheten i Stockholm: 2021/1548-31/1).

RESULTS

Characteristics of the cohort

The most common age periods for having children after an IPI was 30-34 years for both mothers (41%) and fathers (37%) (Table 1). Maternal smoking during pregnancy had a prevalence of 13% overall and was more common in Denmark (16%) than the other countries. The prevalence of maternal smoking during pregnancy was highest for mothers with IPI < 6 months (21%) and IPI ≥ 120 months (24%) (Supplementary Material, Table S2). The proportion of births with parental immigrants varied considerably between countries, from 10% in Finland to 27% in Sweden (20% for the combined cohort). There were slightly more higher-order parity births for the cohort from Finland with 61% of births at parity 1 (*cf.* 66% for the combined cohort) and 10% of births at parity 3 (*cf.* 8% for the combined cohort).

Exposure characteristics – IPI

Although shapes of the IPI distributions were similar, IPIs were shortest in Finland and longest in Sweden (Figure 1). The most common IPI (mode) was 22 months for the cohort from Denmark, 13 months for the cohort from Finland, and 25 months for the cohort from Sweden. The proportion of mothers with more than one IPI varied between countries, from 9% in Sweden and 15% in Denmark, to 23% in Finland and 14% for the combined cohort (Supplementary Material, Table S3).

Outcome characteristics - ASD

There were 9,302 cases of ASD diagnosed among the combined cohort of 925,523 births (Supplementary Material, Table S1). The prevalence of ASD during the study period after an IPI was 10.30 (95% CI: 9.86,

10.75), 5.78 (95% CI: 5.51, 6.05), 12.86 (95% CI: 12.52, 13.20) and 10.05 (95% CI: 9.85, 10.25) cases per 1000 live births in Denmark, Finland, Sweden and the combined cohort, respectively.

Associations between ASD and IPI

In both unadjusted and adjusted analyses there was a U-shaped association between ASD and IPI, which was consistent for all countries (Figure 2). The highest point estimates of unadjusted RRs were for short intervals from Sweden (Supplementary Material, Table S4). After adjustment for covariates the RRs for all IPIs attenuated substantially, overall and by country. Although covariate adjustment attenuated the RRs observed for all IPIs, in Sweden, the RRs remained somewhat higher than those observed from the Denmark and Finland cohorts.

In contrast to the U-shaped association observed between IPI and ASD, there was a monotonic decrease in the covariate adjusted RRs observed with increasing maternal mean IPI (Supplementary Material, Figure S2). After additional adjustment for maternal mean IPI (family cluster adjustment) the observed optimal IPIs decreased by 4 months for the cohort from Denmark and the combined cohort and by 3 months for the cohorts from Finland and Sweden (Table 2). The optimal IPIs after additional maternal mean IPI adjustment were 30 months, 33 months, 39 months, and 35 months in Denmark, Finland, Sweden, and the combined cohort, respectively, although differences in ASD risk across countries was negligible in the IPI range of 30 to 39 months. Family cluster adjustment attenuated the RRs of IPIs shorter than the optimum IPI, but increased the RRs of all IPIs longer than the optimum consistently across all countries (Supplementary Material, Figure S3). For easier visualization of the dynamic shifts in RR at different levels of adjustment, we have produced animation of the transitions in RR by IPI from unadjusted RR, to covariate adjusted RR and finally to covariate plus maternal IPI adjusted RR (Supplementary Material, Animation S1).

Potential Impact Fractions

The PAFs for ASD from non-optimal IPI for Denmark, Sweden and Finland were 9.27% (95% CI: 2.95%, 15.48%), 18.85% (95% CI: 11.11%, 26.13%), and 18.26% (95% CI: 11.89%, 24.44%), respectively (Supplementary Material, Table S5). The PIFs varied both between countries and between scenarios for

change in the IPI distribution (Figure 3). Under the conservative scenario that resulted in fewest mothers adopting the optimal IPI, which excluded all mothers with unintended pregnancies ("unwanted" and "mistimed"), the smallest PIF for ASD was observed for Denmark (4.50%, 95% CI: 1.23%, 7.64%), and the largest PIF was observed for Sweden (8.80%, 95% CI: 5.74%, 11.72%).

Sensitivity Analyses

For all countries, the point estimates from the covariate adjusted analysis after restriction to parity 1 (Table S6) were consistent with those presented in the main analysis (Table 2 and Table S4) after considering the decrease in precision. Point estimates for exposures to long IPIs (120 months) were slightly higher than those from our main results. For Finland, the point estimate for short IPI (3 months) was also slightly higher. Covariate adjusted point estimates for both short and long IPIs for Denmark, and point estimates for short IPIs for Finland were slightly higher from the analysis after restriction to briths from 2003 (Table S7) than those from our main results, although again interval estimates were largely compatible. For Sweden the difference in the results from this sensitivity analysis and our main analysis was negligible. Restriction to births that were not preceded by confirmed diagnosis of an ASD birth (Table S8) and additional adjustment for confirmed diagnosis of a previous ASD birth (Table S9) resulted in point estimates for short intervals that were slightly smaller and point estimates for long intervals that were slightly larger than those from our main results. Similarly, additional adjustment for parental education produced similar results to those from our main analysis (Table S10). Covariate adjusted point estimates after additional adjustment for parental education were higher for short intervals for both countries included in the analysis (Finland and Sweden) and for long intervals were higher for Finland but lower for Sweden. Additional adjustment for marital status resulted in negligible change to the point estimates for both countries included in the analysis (Denmark and Finland), and a large decrease in precision of the combined estimates for both countries together. Restricting the ASD outcome to the autistic disorder subtype (ICD-10 F84.0) resulted in higher covariate adjusted point estimates for short IPI and lower point estimates for long IPI than those for ASD, although interval estimates were compatible (Table S11).

DISCUSSION

We observed consistent U-shaped associations between ASD and IPI for all the countries included (Denmark, Finland and Sweden) that persisted after robust confounder control. Sensitivity analyses also revealed a similar pattern of associations observed for the autistic disorder subtype. We were able to empirically derive the lowest risk for ASD that followed an IPI of 35 months over all countries combined (fully adjusted model), although considering country-level variation, the optimal IPI was within the range of 30 to 39 months. After full adjustment, for the combined cohort from all countries, births that followed an IPI of 3 months had 50% higher risk of ASD and births that followed an IPI of 60 months had 24% higher risk of ASD compared to births at the optimal IPI of 35 months. Importantly, our findings also demonstrate the potential for strong bias and confounding of the IPI-ASD association by both individual- and family-level factors. We observed markedly lower risks at both short and long IPI after adjustment for parental and demographic factors, and even further marked changes after adjustment for maternal mean IPI (family cluster factor) – findings which were also consistent across countries. Although we cannot rule out residual confounding by sociodemographic factors, additional adjustment for parental education and maternal marital status resulted in negligible change to the estimates after taking into consideration the largely consistent interval estimates. There was little evidence for selection bias attributable to between-country differences in parity distributions (e.g., higher order parities in Finland) based on comparison or our main results to those from sensitivity analyses that restricted births to parity 1. The bias attributable to differences in time to observe IPI (e.g., shorter period for Denmark) and bias attributable to differential exclusion of births with missing IPI (e.g., more missing IPIs for Sweden) were both assessed by restriction of the cohort to births from 2003, and indicated no evidence of bias for Sweden. For Denmark, this sensitivity analysis indicated that such bias, if present, would have attenuated our main results for both short an long intervals. Our final bias assessment controlled for confirmed diagnosis of ASD in the previous birth (i.e. older sibling). This was undertaken because parents might delay having another child after already having given birth to a child with ASD. As the incidence of ASD is elevated among siblings we expected this bias to inflate the estimates for longer IPI. However, additional control for

ASD in the previous birth resulted in similar estimates to those from our main results. Taken together, our main results were largely compatible with results from all sensitivity analyses, if not more conservative.

Comparison with other studies

Taken together, results from previous studies indicate U-shaped IPI associations with ASD, albeit based on much smaller samples than the current study.(Cheslack-Postava et al., 2011; K. Cheslack-Postava et al., 2014; Durkin et al., 2015; Gunnes et al., 2013; Zerbo, Yoshida, Gunderson, Dorward, & Croen, 2015) Importantly, our results confirm the shape of this association but suggest that the estimated associations of IPI with ASD are smaller than those described by the previous studies. A study from Wisconsin, USA (31,467 second born children and 160 ASD cases)(Durkin et al., 2015) reported a two-fold increase in risk following an IPI < 12 months compared to an IPI of 24–47 months (OR 2.31, 95%: 1.33, 4.01) and further reported that estimates were sensitive to IPI misclassification resulting from not accounting for previous pregnancy loss,(Durkin et al., 2015) but the magnitude of the bias was small (11% bias in the beta coefficient corresponding to IPIs of >83 months). Another study of 3,137 ASD cases among 662,730 second born children in California, USA reported more than three-fold increases in risk after a short IPI < 12 months compared to a longer IPI of > 36 months (OR 3.39, 95% CI: 3.00, 3.82).(Cheslack-Postava et al., 2011) A later study from a sub-region of the same study location in California reported similar results(Zerbo et al., 2015) and claimed that associations were not mediated by preterm birth or fetal growth restriction. A study from Norway with 223,476 sibling pairs and 966 ASD cases reported a two-fold increase in risk when comparing an of IPI <9 months to an IPI of >36 months (OR 2.18, 95% CI: 1.42, 3.26) and that risk decreased until IPIs of approximately 60 months.(Gunnes et al., 2013) Finally, a study from Finland that matched first and second pregnancies to the same women reported similar associations to our study (OR 1.50, 95% CI 1.28, 1.74 for IPI < 12 months, compared to a referent IPI of 24 –59 months).(K. Cheslack-Postava et al., 2014).

We included higher order births than previous studies which allowed us to calculate the maternal mean IPI for families with more than two children in the study. By adjusting for the maternal mean IPI, our study controlled for the propensity of observing specific IPIs, which had a marked effect on the observed association between IPI and risk of ASD. Associations between ASD and maternal mean IPI (Figure S3) indicated that mothers who had *shorter* mean IPIs than the optimal IPI had greater propensity to have a child with ASD and that

mothers with *longer* mean IPIs than the optimal had lower propensity to have a child with ASD. Consequently, when we did not adjust for mean IPI the RRs observed for shorter IPI were inflated whereas the RRs for longer IPIs were deflated. Caveats on the usefulness of adjustment for maternal mean IPI are that it necessarily produces overly conservative estimates as it partially adjusts for the exposure of interest, and maternal mean IPI relies on having more than one IPI, which can lead to imprecise estimates. For this reason we reported estimates with and without adjustment for maternal mean IPI.

Biological plausibility of IPI effects

Several authors have proposed that transient nutritional depletion, particularly folate depletion, as a notable plausible biological pathway that might explain effects of shorter IPIs(Schmidt et al., 2011) on ASD risk. It remains unclear as to whether these effects would attenuate with micronutrient supplementation alone. Folate supplementation prior to and in early pregnancy is a common public health advisory and clinical practice standard. Many factors could affect adherence to such practice and not all pregnancies are planned, especially perhaps those with a short IPI. Associations observed for long intervals might occur if physiological and anatomical capacities promoted by a prior pregnancy, such as improved uterine blood flow,(Resnik, 1984) decline over time, ultimately resulting in regression to a primigravid state.(Conde-Agudelo et al., 2012) A higher risk for miscarriage in older mothers might lead to longer IPIs in our data, especially as we did not have data on intervening pregnancies that did not terminate with a livebirth. Advanced parental age might also be a contributing factor to ASD risk, although we accounted for parental age in our analysis. Older mothers might be more likely to seek fertility treatment. Subfecundity and fertility treatment could be associated with longer IPI but the evidence for association with ASD is not well-established,(Conti, Mazzotti, Calderoni, Saviozzi, & Guzzetta, 2013) although newer reviews indicate the plausibility of an association.(Gao, He, Cai, Wang, & Fan, 2017) Lactational amenorrhea is another important factor influencing IPI and there is some research pointing towards longer breastfeeding duration being associated with fewer autistic traits,(Boucher et al., 2017) but autistic traits are an imperfect proxy for incident cases and further research is needed to

confirm such associations. Factors leading to long IPIs, especially over 60 months, are undoubtedly complex and include both biologic and social contributors possibly associated with ASD risk.

If ASD associations were solely attributable to biological mechanisms, unconfounded by unmeasured factors, we would expect the RRs and optimal IPI observed in our study to be the same between the three countries. The shape of the ASD-IPI associations in the fully adjusted analyses were similar between countries but between-country variation in RR was larger than within-country variation and we attribute such variation to unaccounted differences in country-specific traits and processes that promote certain IPIs for mothers with particular risk profiles. For example, the maximum amount of paid maternity and parental leave for mothers after delivery is 46 weeks in Denmark, 47 weeks in Finland, and 92 weeks in Sweden. Longer parental leave encourages longer breastfeeding duration. Longer paid parental leave in Sweden might also have contributed to the relatively smaller proportion of births with shorter IPIs in Sweden, among which there may have been a relatively greater proportion of unintended pregnancies. If unintended pregnancy is a risk factor for ASD, this might explain the higher RRs of short IPIs for Sweden compared to Denmark and Finland.

Clinical relevance

Under the scenario that the IPI-ASD association is causal and IPI for intended pregnancies is modifiable, approximately 5%, 8% and 9% of ASD cases could be potentially avoided by adopting optimal IPIs in Denmark, Finland and Sweden, respectively. However, as these results are derived from our observational study, there remains a degree of uncertainty as to whether counselling families to target a 30- to 39-month IPI range would achieve such reductions in ASD incidence if IPI is not a causal factor. Post-partum IPI counselling is further complicated by the increased risk of ASD associated with parental biological aging;(Sandin et al., 2016) age-related fertility decline; the possibility that effects of IPI might differ after pregnancy loss, as has been observed for other endpoints;(Regan et al., 2019) different optimal IPIs for other outcomes, such as 18-24 months to avoid preterm birth and fetal growth restriction;(Ball, Pereira, Jacoby, De Klerk, & Stanley, 2014) and the expected time taken to become pregnant from first pregnancy attempt, which is typically less than 12 months for more than 80% of mothers.(Juul, Karmaus, & Olsen, 1999) Given the

multiple closely related biological and social pathways, a holistic approach to post-partum counselling to minimise the risk of unintentional pregnancy and avoid intentional entry into parenthood at advanced maternal age is warranted. Such counselling would minimise risk from pathways involving parental aging, either directly through age-related fertility decline or intended short IPI at advanced maternal age, and associations with ASD directly affected or mediated by these factors.

Limitations

Because a randomized trial would not be feasible, or indeed ethical, we conducted an observational study and therefore cannot rule out the possibility of residual confounding. We did not have information on whether the pregnancies included in this study were intended. Approximately one quarter of pregnancies are unintended.(Juul et al., 1999) Unmeasured factors, such as subclinical parental psychiatric history, parental subfertility and pregnancy intention, might be associated with ASD and thereby disproportionately contribute to the number of IPIs at both tails of the distribution. Our study incompletely controlled for the genetic inheritance of ASD. We assumed that the genetic inheritance of ASD could not confound associations because child genetic predisposition to ASD cannot affect IPI conditional on our adjustment variables. We did not have information on fertility treatment or breastfeeding duration. We attempted to minimise residual confounding by adjustment for maternal mean IPI as a proxy for factors that predispose mothers to a particular IPI. As under-five child mortality in the study countries is low (≤3.8 per 1000 live births) we do not expect substantial selection bias by differential survival.(UN Inter-agency Group for Child Mortality Estimation, 2019) Misclassification of IPI due to an unobserved intervening pregnancy might have led to an overestimation of RR for longer IPIs. However, such bias could be small because nutritional depletion might be low after miscarriage, which reaches its peak close to the end of the first trimester (10 – 12 weeks) when the placental function has only just commenced and the fetal size is small (<100 grams).(Goldhaber & Fireman, 1991; Kiserud et al., 2018) Our results are not necessarily generalizable to low-income countries, nor to high-income countries with higher fertility rates, and greater socioeconomic and health inequity.

Conclusions

In the high income countries of this study, which provide universal health care and paid parental leave after childbirth, there was a consistent elevated risk of ASD associated with both short and long IPIs beyond the optimal range of 30-39 months. However, we observed potential for strong bias and confounding of the IPI-ASD association by both individual- and family-level factors. Causal factors which might account for the association between IPI and ASD, and therefore serve as potential preventive targets, are not well-established. Nevertheless, if there is a causal link, a notable fraction of ASD cases might be attributable to sub-optimal IPI. Fortunately, IPI is modifiable. Counselling families to avoid both sub-optimal IPIs and their indications, such as unintended pregnancy and delayed age at first pregnancy, has the potential to prevent a proportion of ASD cases.

Contributorship

GP conceived the study, conducted statistical analysis and drafted the first manuscript. All authors contributed to interpretation of results, updates of the manuscript, and revision of methods.

References

Ahrens, K. A., Thoma, M. E., Copen, C. E., Frederiksen, B. N., Decker, E. J., & Moskosky, S. (2018). Unintended pregnancy and interpregnancy interval by maternal age, National Survey of Family Growth. *Contraception*, *98*(1), 52-55.

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. *BMJ, 349*, g4333.

Begg, M. D., & Parides, M. K. (2003). Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Statistics in Medicine, 22*(16), 2591-2602. doi:10.1002/sim.1524

Boucher, O., Julvez, J., Guxens, M., Arranz, E., Ibarluzea, J., Sánchez de Miguel, M., . . . Sunyer, J. (2017). Association between breastfeeding duration and cognitive development, autistic traits and ADHD symptoms: a multicenter study in Spain. *Pediatr Res, 81*(3), 434-442. doi:10.1038/pr.2016.238

Cheslack-Postava, K., Jokiranta, E., Suominen, A., Lehti, V., Sourander, A., & Brown, A. S. (2014). Variation by Diagnostic Subtype in Risk for Autism Spectrum Disorders Associated with Maternal Parity among Finnish Births. *Paediatric and Perinatal Epidemiology, 28*(1), 58-66. doi:https://doi.org/10.1111/ppe.12094

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.

Cheslack-Postava, K., Suominen, A., Jokiranta, E., Lehti, V., McKeague, I. W., Sourander, A., & Brown, A. S. (2014). Increased risk of autism spectrum disorders at short and long interpregnancy intervals in Finland. *J Am Acad Child Adolesc Psychiatry, 53*(10), 1074-1081.e1074. doi:10.1016/j.jaac.2014.06.009

Class, Q. A., Rickert, M. E., Larsson, H., Öberg, 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. doi:10.1093/ije/dyy042

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), e20153482. doi:10.1542/peds.2015-3482

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.

Conti, E., Mazzotti, S., Calderoni, S., Saviozzi, I., & Guzzetta, A. (2013). Are children born after assisted reproductive technology at increased risk of autism spectrum disorders? A systematic review. *Human reproduction, 28*(12).

Dodds, L., Fell, D. B., Shea, S., Armson, B. A., Allen, A. C., & Bryson, S. (2011). The role of prenatal, obstetric and neonatal factors in the development of autism. *Journal of autism and developmental disorders, 41*(7), 891-902.

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.

Gao, J., He, X., Cai, Y., Wang, L., & Fan, X. (2017). Association between assisted reproductive technology and the risk of autism spectrum disorders in the offspring: a meta-analysis. *Scientific reports, 7*, 46207.

Goldhaber, M. K., & Fireman, B. H. (1991). The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. *Epidemiology*, 33-39.

Gunnes, N., Surén, P., Bresnahan, M., Hornig, M., Lie, K. K., Lipkin, W. I., . . . Schjølberg, S. (2013). Interpregnancy interval and risk of autistic disorder. *Epidemiology*, 906-912.

Hansen, S. N., Schendel, D. E., Francis, R. W., Windham, G. C., Bresnahan, M., Levine, S. Z., . . . Parner, E. T. (2019). Recurrence Risk of Autism in Siblings and Cousins: A Multinational, Population-Based Study. *Journal of the American Academy of Child & Adolescent Psychiatry, 58*(9), 866-875. doi:https://doi.org/10.1016/j.jaac.2018.11.017

Juul, S., Karmaus, W., & Olsen, J. (1999). Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. *Human reproduction, 14*(5), 1250-1254.

Kiserud, T., Benachi, A., Hecher, K., Perez, R. G., Carvalho, J., Piaggio, G., & Platt, L. D. (2018). The World Health Organization fetal growth charts: concept, findings, interpretation, and application. *American Journal of Obstetrics and Gynecology, 218*(2, Supplement), S619-S629. doi:https://doi.org/10.1016/j.ajog.2017.12.010

Marston, C. (2006). Report of a technical consultation on birth spacing, Geneva, 13-15 June 2005.

Newschaffer, C. J., Croen, L. A., Daniels, J., Giarelli, E., Grether, J. K., Levy, S. E., . . . Reaven, J. (2007). The epidemiology of autism spectrum disorders. *Annu. Rev. Public Health, 28*, 235-258.

Regan, A. K., Gissler, M., Magnus, M. C., Håberg, S. E., Ball, S., Malacova, E., . . . Pereira, G. (2019). Association between interpregnancy interval and adverse birth outcomes in women with a previous stillbirth: an international cohort study. *The Lancet, 393*(10180), 1527-1535.

Resnik, R. (1984). Gestational changes of the reproductive tract and breasts. *Maternal-Fetal Medicine Principle and Practice. Philadelphia WB Saunders*, 141-179.

Riley, R. D., Lambert, P. C., & Abo-Zaid, G. (2010). Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ, 340*, c221. doi:10.1136/bmj.c221

Robinson, W. (1950). 1950" Ecological correlations and the behavior of individuals", American Sociological Review 15: 351-357.

Sandin, S., Schendel, D., Magnusson, P., Hultman, C., Surén, P., Susser, E., . . . Gross, R. (2016). Autism risk associated with parental age and with increasing difference in age between the parents. *Molecular psychiatry, 21*(5), 693-700.

Schendel, D. E., Bresnahan, M., Carter, K. W., Francis, R. W., Gissler, M., Grønborg, T. K., . . . Hultman, C. M. (2013). The International Collaboration for Autism Registry Epidemiology (iCARE): multinational registry-based investigations of autism risk factors and trends. *Journal of autism and developmental disorders, 43*(11), 2650-2663.

Schmidt, R. J., Hansen, R. L., Hartiala, J., Allayee, H., Schmidt, L. C., Tancredi, D. J., . . . Hertz-Picciotto, I. (2011). Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. *Epidemiology, 22*(4), 476-485. doi:10.1097/EDE.0b013e31821d0e30

Thomas, D., Radji, S., & Benedetti, A. (2014). Systematic review of methods for individual patient data meta-analysis with binary outcomes. *BMC medical research methodology, 14*, 79-79. doi:10.1186/1471-2288-14-79

UN Inter-agency Group for Child Mortality Estimation. (2019). World Development Indicators: Mortality rate, under-5 (per 1,000 live births). *DataBank World Development Indicators, Source: databank.worldbank.org/source/world-development-indicators/preview/on*.

Wood, S. N. (2011). Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology), 73*(1), 3-36.

Wood, S. N. (2017). *Generalized additive models: an introduction with R*: CRC press.

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. doi:10.1542/peds.2015-1099

Table 1. Characteristics of the study population of 925,523 births from Denmark, Finland and Sweden

	Denmark		Finland		Sweden		All countries	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Maternal age								
≤ 19 years	176	0.09	450	0.15	975	0.23	1601	0.17
20 – 24 years	9515	4.79	24281	8.22	29250	6.78	63046	6.81
25 – 29 years	49190	24.76	77558	26.26	116136	26.92	242884	26.24
30 – 34 years	90362	45.48	108852	36.85	177350	41.11	376564	40.69
35 – 39 years	42843	21.56	67138	22.73	91638	21.24	201619	21.78
≥ 40 years	6607	3.33	17110	5.79	16092	3.73	39809	4.3
Paternal age								
≤ 19 years	31	0.02	181	0.06	321	0.07	533	0.06
20 – 24 years	3012	1.52	11352	3.84	11417	2.65	25781	2.79
25 – 29 years	27326	13.75	54102	18.32	73595	17.06	155023	16.75
30 – 34 years	79147	39.83	99628	33.73	161139	37.35	339914	36.73
35 – 39 years	61673	31.04	82952	28.08	121475	28.16	266100	28.75
≥ 40 years	27504	13.84	47174	15.97	63494	14.72	138172	14.93
Maternal smoking								
No	167290	84.20	254732	86.24	387207	89.75	809229	87.43
Yes	31403	15.80	40657	13.76	44234	10.25	116294	12.57
Immigrant								
No	161933	81.50	267177	90.45	315535	73.14	744645	80.46
Yes	36760	18.50	28212	9.55	115906	26.86	180878	19.54
Parental psychiatric history								
No	151500	76.25	229887	77.83	326916	75.77	708303	76.53
Yes	47193	23.75	65502	22.17	104525	24.23	217220	23.47
Parity								
1 (2nd birth)	138964	69.94	180820	61.21	289689	67.14	609473	65.85
2 (3rd birth)	47197	23.75	84876	28.73	110442	25.60	242515	26.20
3 (4th birth)	12532	6.31	29693	10.05	31310	7.26	73535	7.95
Number of siblings in the cohort [1]								
No siblings	144332	72.64	179760	60.86	359169	83.25	683261	73.82
1 sibling	48566	24.44	91098	30.84	64652	14.99	204316	22.08
2 siblings	5739	2.89	24531	8.30	7620	1.77	37890	4.09
3 siblings	56	0.03	0	0	0	0	56	0.01
Follow-up time								
5 – 7 years	60226	30.31	59634	20.19	103025	23.88	222885	24.08
8 – 10 years	83870	42.21	87754	29.71	143251	33.2	314875	34.02
11 – 13 years	52311	26.33	87680	29.68	121142	28.08	261133	28.21
14 – 15 years	2286	1.15	60321	20.42	64023	14.84	126630	13.68
Year of birth								

1998	9	0.00	30056	10.18	31218	7.24	61283	6.62
1999	2277	1.15	30265	10.25	32805	7.60	65347	7.06
2000	10503	5.29	29758	10.07	37611	8.72	77872	8.41
2001	18607	9.36	29258	9.90	40384	9.36	88249	9.54
2002	23201	11.68	28664	9.70	43147	10.00	95012	10.27
2003	26229	13.20	28962	9.80	45899	10.64	101090	10.92
2004	28097	14.14	29482	9.98	48271	11.19	105850	11.44
2005	29544	14.87	29310	9.92	49081	11.38	107935	11.66
2006	30200	15.20	29851	10.11	51294	11.89	111345	12.03
2007	30026	15.11	29783	10.08	51731	11.99	111540	12.05
Interpregnancy Interval (IPI)								
< 6 months	7499	3.77	10424	3.53	2046	0.47	19969	2.16
6 – 11 months	24772	12.47	40972	13.87	10671	2.47	76415	8.26
12 – 17 months	33171	16.69	47626	16.12	32675	7.57	113472	12.26
18 – 23 months	35431	17.83	38274	12.96	61495	14.25	135200	14.61
24 – 59 months	86710	43.64	103911	35.18	229626	53.22	420247	45.41
60 – 119 months	11110	5.59	42206	14.29	76085	17.64	129401	13.98
≥ 120 months	NA	NA	11976	4.05	18843	4.37	30819	3.33
Maternal mean IPI [2]								
< 6 months	4578	2.30	4741	1.61	223	0.05	9542	1.03
6 – 11 months	19787	9.96	29065	9.84	3201	0.74	52053	5.62
12 – 17 months	33332	16.78	45844	15.52	27594	6.40	106770	11.54
18 – 23 months	39476	19.87	44420	15.04	65905	15.28	149801	16.19
24 – 59 months	92004	46.30	123227	41.72	243549	56.45	458780	49.57
60 – 119 months	9516	4.79	37976	12.86	72126	16.72	119618	12.92
≥ 120 months	NA	NA	10116	3.42	18843	4.37	28959	3.13

1. Number of siblings in the cohort that follow an IPI
2. Maternal mean IPI is the arithmetic mean of all IPIs for children in the cohort, by mother.

Table 2. Adjusted Relative Risk of ASD for selected IPIs compared to optimal IPIs observed for Denmark, Finland, Sweden and the combined cohort at which risk was minimised.

	Denmark		Finland		Sweden		All countries	
IPI	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
	Covariate adjusted [1]							
3 months	1.39	(1.23, 1.57)	1.57	(1.40, 1.78)	2.05	(1.83, 2.30)	1.63	(1.21, 2.22)
6 months	1.32	(1.19, 1.47)	1.48	(1.33, 1.65)	1.89	(1.71, 2.08)	1.53	(1.16, 2.02)
12 months	1.21	(1.12, 1.30)	1.31	(1.20, 1.42)	1.60	(1.48, 1.72)	1.35	(1.08, 1.70)
18 months	1.11	(1.05, 1.18)	1.17	(1.10, 1.26)	1.37	(1.28, 1.46)	1.21	(1.01, 1.44)
24 months	1.04	(1.00, 1.09)	1.08	(1.02, 1.13)	1.20	(1.13, 1.26)	1.10	(0.97, 1.25)
Optimal IPI	Ref	IPI: 34 months	Ref	IPI: 36 months	Ref	IPI: 42 months	Ref	IPI: 39 months
48 months	1.06	(1.00, 1.13)	1.06	(1.01, 1.11)	1.02	(1.00, 1.04)	1.03	(0.96, 1.12)
60 months	1.19	(1.06, 1.32)	1.21	(1.10, 1.32)	1.14	(1.07, 1.20)	1.15	(0.95, 1.37)
120 months[3]	1.16	(0.73, 1.86)	1.78	(1.49, 2.12)	1.59	(1.42, 1.79)	1.40	(0.72, 2.64)
	Covariate and cluster adjusted [2]							
3 months	1.28	(1.12, 1.46)	1.47	(1.29, 1.67)	1.89	(1.66, 2.16)	1.50	(1.11, 2.03)
6 months	1.23	(1.10, 1.37)	1.38	(1.23, 1.55)	1.74	(1.56, 1.96)	1.41	(1.08, 1.86)
12 months	1.13	(1.05, 1.23)	1.24	(1.13, 1.35)	1.49	(1.36, 1.63)	1.26	(1.02, 1.57)
18 months	1.06	(1.01, 1.12)	1.12	(1.05, 1.20)	1.28	(1.19, 1.39)	1.14	(0.97, 1.34)
24 months	1.02	(0.99, 1.05)	1.04	(1.00, 1.09)	1.14	(1.07, 1.21)	1.06	(0.95, 1.18)
Optimal IPI	Ref	IPI: 30 months	Ref	IPI: 33 months	Ref	IPI: 39 months	Ref	IPI: 35 months
48 months	1.13	(1.03, 1.23)	1.11	(1.03, 1.19)	1.05	(1.01, 1.09)	1.08	(0.95, 1.22)
60 months	1.31	(1.14, 1.50)	1.31	(1.16, 1.47)	1.22	(1.12, 1.33)	1.24	(0.98, 1.57)
120 months[3]	1.54	(0.89, 2.67)	2.36	(1.79, 3.09)	2.15	(1.67, 2.77)	1.85	(0.85, 3.84)

1. Adjusted for covariates: parity (categorised as 2nd, 3rd, 4th birth), spline functions of maternal and paternal ages, an indicator for at least one parent born outside the cohort country, an indicator for maternal smoking during pregnancy, parental history of psychiatric diagnoses, year of birth, and follow-up.

2. Adjusted for covariates listed above and maternal mean IPI

3. Note that RRs can be calculated based on the estimated spline functions although there were no births that occurred at or after IPIs of 120 months in the cohort from Denmark.

Figure 1. Empirical distribution of Interpregnancy Interval (IPI) by country for IPIs up to 120 months

Figure 2. Fully adjusted Relative Risk (RR) [1] of ASD and 95% Confidence Interval bands relative to Interpregnancy Interval (IPI) at which the minimum risk was observed in each country (optimal IPI).

1. Adjustment: parity (categorised as 2nd, 3rd, 4th birth), spline functions of maternal and paternal ages, an indicator for at least one parent born outside the cohort country, an indicator for maternal smoking during pregnancy, parental history of psychiatric diagnoses, year of birth, follow-up time and maternal mean IPI

Figure 3. Percentage reduction in ASD under various counterfactual scenarios for change in the IPI distribution, with 95% Centile Intervals. Scenarios based on compliance: (i) 100%, (ii) 90%, and (iii) 75% of mothers adopt the optimal IPI. Scenarios based on exclusions: mothers with unintended pregnancies that were (i) "unwanted," and (ii) were "unwanted" or "mistimed", do not adopt the optimal IPI.[1]

1. Conservative centile intervals: The lower and upper limits are the PAFs corresponding to the 2.5th and 97.5th centiles of RR, based on 10,000 simulations from the RR distribution for each country and discrete month of IPI.
2. See the Supplementary Material for further information on calculation of the PIFs, CIs, and the proportions of births assumed to be "unwanted" or "mistimed" by IPI month.