The association between the interpregnancy interval and autism spectrum disorder in a Canadian cohort

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ABSTRACT

OBJECTIVES: Two studies reported an increased risk of autistic disorder in children conceived less than 12 months after a previous birth. Our objective was to examine the association between the interpregnancy interval (IPI) and autism spectrum disorder (ASD) in a Canadian cohort.

METHODS: Using administrative datasets housed at the Manitoba Centre for Health Policy, we identified pairs of first- and second-born singleton siblings born between 1988 and 2005. Diagnoses of ASD were ascertained by searching physician billing claims, hospital discharge abstracts, education data, and a database containing information on individuals identified for a 2002–2007 ASD surveillance program in Manitoba. Logistic regression models were fit to examine the association between the IPI and ASD in 41,050 second-born siblings where the first-borns did not have ASD, using IPIs of ≥36 months as the reference category and specifying three case groups. Case Group 1 included individuals with at least one ASD code (n = 490); Case Group 2 included those with two or more ASD codes (n = 375); and Case Group 3 comprised individuals with a record in the ASD surveillance program database (n = 141).

RESULTS: The adjusted odds ratios (ORs) for IPIs shorter than 12 months ranged from 1.22 (95% CI: 0.91–1.63) for Case Group 1 to 1.72 (95% CI: 0.96–3.06) for Case Group 3. When the case groups were restricted to individuals with more severe ASD, the ORs increased and were significant for Case Groups 1 and 2.

CONCLUSION: Our findings also support an association between short IPIs and more severe ASD.

KEY WORDS: Autism; interpregnancy interval; secondary analysis; administrative data; record linkage; Manitoba Centre for Health Policy

La traduction du résumé se trouve à la fin de l'article.

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Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder. Twin studies provide evidence of moderate-to-high heritability,[1,2] but environmental factors also influence risk.[2] The increasing prevalence[3,4] and substantial economic burden[5] of ASD form a strong rationale for investigating potentially modifiable risk factors.

Two studies[6,7] have reported an increased risk of autism* associated with short interpregnancy intervals (IPIs, defined as the length of time between the end of one pregnancy and the beginning of subsequent gestation). In the first of these studies,[6] researchers identified pairs of first and second singletons born to the same parents in California from 1992 through 2002. Case status was assigned by searching for codes corresponding to "autism, full syndrome" or "autism, residual state" in California's Department of Developmental Services electronic file. An inverse association between the IPI and autism was observed among 662,730 second-born children, with the highest risk reported for intervals shorter than 12 months as compared to 36 months or more. More recently, investigators analyzed data from a Norwegian birth cohort of first- and second-born singleton full siblings.[7] ASD diagnoses were ascertained through the Norwegian Patient Registry. IPIs shorter than 12 months were associated with an increased risk of autistic disorder among 223,476 second-born children.

Prenatal nutritional status has been linked to brain development in the offspring,[8–11] which supports a potential biologic basis for the association between short IPIs – which may contribute to maternal nutritional depletion[12] – and autism/ASD. If this or some other biologic mechanism underlies the observed associations, rather than confounding or chance, it would open up opportunities for modifying risk. To add to the emerging epidemiologic evidence, this retrospective cohort

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Conflict of Interest: None to declare.

*In this paper, "autism" is a generic term for a more severe form of ASD, including autistic disorder, while "ASD" refers to the entire autism spectrum.

study examined the association between the IPI and ASD in a Manitoba birth cohort.

METHODS

This study was approved by research ethics boards at Queen's University and the University of Manitoba, and Manitoba's Health Information Privacy Committee. Approvals were also granted by Manitoba Education and Manitoba Family Services for the use of their data.

Data sources

The Population Health Research Data Repository at the Manitoba Centre for Health Policy (MCHP) houses linkable databases that contain health and other information collected for administrative purposes. A unique encrypted personal health identification number is attached to each record in the Repository databases; this system maintains privacy and confidentiality while ensuring the accurate matching of records across databases.[13]

Five Repository databases were used for this study: 1) **Medical Services** (physician claims, which are submitted by fee-for-service physicians and by those compensated through alternative payment mechanisms; one "most responsible" diagnosis is recorded to the third digit of the ICD-9-CM); 2) **Hospital Discharge Abstracts** (records related to admissions to acute and chronic care facilities, and out-patient surgeries provided in a hospital setting; a maximum of 16 diagnoses are coded to the fifth digit of the ICD-9-CM for encounters up to March 31, 2004, and a maximum of 25 diagnoses are coded to the fifth digit of the ICD-10 thereafter); 3) **Education** (enrollment and assessment information from 1995 onwards for kindergarten through Grade 12 students, including those who attend private schools or are home-schooled; a nominal variable indicates whether a child received funding under a special needs category); 4) **Social Assistance Management Information Network** (data from 1995 onwards to indicate whether an individual received income assistance in a particular month and year); and 5) **Manitoba Health Insurance Registry** (dates of birth, death, and moves within and to and from the province for all individuals covered under Manitoba's health plan). We also obtained permission to use a sixth data source, the **Children's Special Services dataset**, which was created and brought into the Repository for another project led by one of the investigators (H. Ouellette-Kuntz). That dataset contained information on children and youth who, as part of a larger Canadian epidemiologic study[14] (www.nedsac.ca), were identified for an ASD surveillance program in Manitoba from 2002–2007 through Children's Special Services, a provincial government program that supports children with special needs throughout Manitoba (with the exception of those living on First Nations reserves). Proof of a diagnosis made by a qualified health professional (e.g., developmental pediatrician, psychologist, psychiatrist) is required to access program services related to ASD.[14]

Study cohort and case definitions

Individuals born in Manitoba between January 1, 1988 and March 31, 2005 were identified from hospital records, and the Manitoba Health Insurance Registry was used to identify first and second births to the same mother (i.e., first- and second-born sibling pairs). We ascertained ASD case status by searching up to March 31, 2011 for relevant diagnostic codes in the Medical Services (ICD-9 code 299) and Hospital Discharge Abstracts (ICD-9 codes 299.0, 299.8, 299.9; ICD-10 codes F84.0, F84.1, F84.5, F84.8, F84.9) databases, or an "ASD" special needs designation in the Education data. Individuals were also considered to have ASD if they had a record in the Children's Special Services dataset (collectively, these criteria are referred to as "ASD codes"). The IPI was calculated as the interval between the birthdates of the two siblings minus the younger sibling's gestational age at birth in completed weeks.

The sensitivity and specificity of the codes used to identify cases of ASD in Manitoba's administrative health and education data have not been evaluated. Accordingly, we applied three case definitions to better interpret the findings. **Case Group 1** included any individual for whom at least one ASD code was found. The other two case groups were subsets of Case Group 1. **Case Group 2** included individuals with two or more ASD codes (at least two codes in the Medical Services, Hospital Discharge Abstracts, or Education data, or at least one code in two or more databases, including the Children's Special Services dataset). **Case Group 3** included individuals with a record in the Children's Special Services dataset. As previously described, these individuals were identified for an ASD surveillance program in Manitoba. Our assumption was that the proportion of true positives (i.e., individuals with ASD) would differ in a predictable manner across the groups. Based on algorithms that have been tested to identify other conditions using administrative data,[15] we assumed that Case Group 2 would have a higher proportion of true positives than Case Group 1, and that all individuals in Case Group 3 would have ASD. If the IPI is associated with ASD, we would therefore expect to see the weakest effect in Case Group 1 and the strongest in Case Group 3.

Multiple births were excluded from the study cohort, as were sibling pairs where both children did not reside continuously in Manitoba until at least their sixth birthday (to ensure diagnoses were not missed because they were made outside Manitoba, and because 12% of children with an administrative diagnosis of ASD are only captured in the Education data[16]). Sibling pairs were also excluded if the mother was living in a First Nations community when the second child was born. This was to ensure comparability of the findings for the three case groups; the Children's Special Services dataset did not capture cases of ASD among children living on reserves. Other exclusion criteria included sibling pairs where the gestational age was missing for the younger sibling or where the calculated IPI had a negative value, and sibling pairs where an ASD code was found for the first-born child. We restricted the cohort for the main analysis to sibling pairs where there was no record of a pregnancy loss or termination between the two births, as an association between the IPI and ASD may be mediated by maternal physiologic parameters during pregnancy.[6,17] Since our calculation of the IPI was based on live births, the impact of intervals of equal length may not be comparable if a pregnancy loss or termination occurred between some births.

Analysis

The data were analyzed at MCHP using SAS 9.3 (SAS Institute Inc., Cary, NC). The IPI was converted into months and similar categories to those analyzed in the California and Norwegian studies were specified (<12, 12–23, 24–35, ≥36 (reference)).[6,7] Separate logistic regression models were fit for each case group to estimate crude and adjusted odds ratios (ORs) for ASD in the second-born children, using the same comparison group in each model. A priori, we decided to include the following covariates in the models due to previously documented associations with ASD: child's sex, birth year (we mean-centered this variable and created a quadratic term to account for birth year's non-linear association with ASD in our cohort), and presence of an intellectual disability (defined as a "Multiple Handicaps" special needs code in the Education data, or the presence of various diagnostic codes in the Medical Services or Hospital Discharge Abstracts databases[18]), as well as maternal age at delivery (<30, 30–34, ≥35 years[19–21]) and whether the mother had ever received income assistance. In a supplementary analysis, we added product terms to the regression models to explore whether certain factors interacted with the IPI to modify the association. Those factors included the child's sex, whether he or she had an intellectual disability, or was born in 1998 or earlier (Canada instituted a mandatory folic acid fortification program for white flour and enriched grain products in 1998), and maternal age.

We performed several sensitivity analyses to assess whether methodological factors might explain any difference between our findings and those of the California[6] and Norwegian[7] studies. In the main analysis, we excluded sibling pairs where a pregnancy loss or termination was reported between the two births; this was not done in the other studies. In the first sensitivity analysis ("Sensitivity Analysis 1"), we included second-born children from these sibling pairs.

The California study examined the association between the IPI and autism.[6] The Norwegian cohort included cases across the spectrum, but their main outcome was autistic disorder.[7] There was no direct measure of ASD severity for many of our cases (the Education data indicate whether a child was approved for Level 2 support for "moderate ASD" or Level 3 support for "severe to profound ASD,"[22] but only about 60% of cases were identified in that source (data not shown)). A previous study reported that the median age at diagnosis of autistic disorder in Manitoba was 42 months, compared to 77 months for pervasive developmental disorder, not otherwise specified (PDD-NOS) and 101 months for Asperger disorder.[23] As a proxy measure of greater severity then, we restricted the case groups to individuals diagnosed before 42 months of age, or to those with an "ASD" code in the Education data who were approved for Special Needs Level 2 or Level 3 funding ("Sensitivity Analysis 2"). These individuals are referred to as "more severe" cases throughout the remainder of this paper, with the quotation marks retained to indicate the proxy nature of this designation.

All references to significance are based on a p-value of <0.05.

RESULTS

A total of 66,355 sibling pairs were initially identified. After the exclusion criteria were applied, 41,050 pairs remained for the main analysis (Figure 1). Of those, 40,560 were pairs where the younger sibling had no record of an ASD diagnosis. There were 490 cases in Case Group 1; 375 in Case Group 2; and 141 in Case Group 3.

Table 1 shows the distribution of the IPI and characteristics of the second-born children in the study cohort. All three case groups had a higher proportion of boys and individuals with an intellectual disability than the comparison group. The IPI distribution was fairly similar across all groups.

Table 2 provides crude and adjusted ORs for the association between the IPI and ASD in the second-born children. While a test for linear trend approached significance for Case Groups 2 and 3, we did not additionally model the IPI as a continuous variable as there was no evidence of a stronger association for shorter intervals within each IPI category (data not shown).

Figures 2 and 3 illustrate the results of the sensitivity analyses (shown for IPIs of <12 and 12–23 months only). There was little

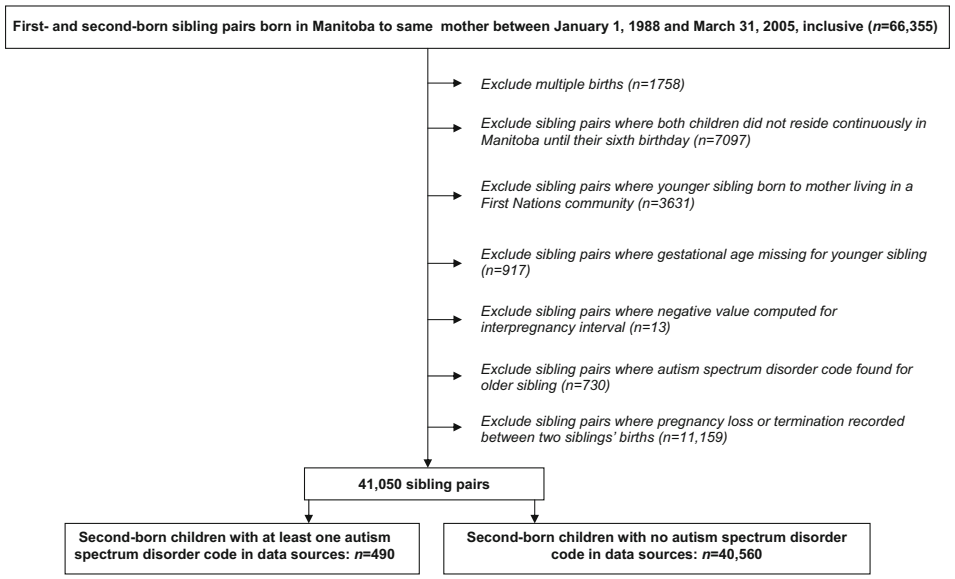

Figure 1. Selection of study cohort for main analysis

Table 1. Characteristics of second-born children from sibling pairs born to the same mother in Manitoba between January 1, 1988 and March 31, 2005, where no record of autism spectrum disorder was found for first-born siblings

	Second-born children with at least one ASD code			Second-born children with no ASD code (*n* = 40,560)
	Case Group 1* (*n* = 490)	Case Group 2† (*n* = 375)	Case Group 3‡ (*n* = 141)	
Interpregnancy interval in months, *n* (%)				
<12	125 (25.5)	99 (26.4)	38 (27.0)	9545 (23.5)
12–23	179 (36.5)	141 (37.6)	59 (41.8)	15,571 (38.4)
24–35	95 (19.4)	70 (18.7)	24 (17.0)	7968 (19.6)
≥36	91 (18.6)	65 (17.3)	20 (14.2)	7476 (18.4)
Boy, *n* (%)	380 (77.6)	303 (80.8)	114 (80.9)	20,599 (50.8)
Year of birth, *n* (%)				
1988–1992	80 (16.3)	63 (16.8)	29 (20.6)	7910 (19.5)
1993–1996	152 (31.0)	126 (33.6)	53 (37.6)	11,858 (29.2)
1997–2000	136 (27.8)	98 (26.1)	35 (24.8)	10,474 (25.8)
2001–2005	122 (24.9)	88 (23.5)	24 (17.0)	10,318 (25.4)
Intellectual disability (child), *n* (%)	120 (24.5)	97 (25.9)	54 (38.3)	464 (1.1)
Maternal age at delivery,§ years, *n* (%)				
≥35	61 (12.4)	46 (12.3)	25 (17.7)	4074 (10.0)
30–34	167 (34.1)	136 (36.3)	57 (40.4)	12,173 (30.0)
<30	262 (53.5)	193 (51.5)	59 (41.8)	24,312 (59.9)
Ever receipt of income assistance (mother), *n* (%)	105 (21.4)	82 (21.9)	24 (17.0)	6220 (15.3)
"More severe" cases,‖ *n* (%)	338 (69.0)	310 (82.7)	132 (93.6)	–

ASD: Autism spectrum disorder.

*At least one ASD code in any of the following databases: Medical Services, Hospital Discharge Abstracts, Education, or Children's Special Services dataset.

†At least two ASD codes in one of the following databases: Medical Services, Hospital Discharge Abstracts, or Education; or at least one ASD code in two or more of the following databases: Medical Services, Hospital Discharge Abstracts, Education, or Children's Special Services dataset.

‡Record in the Children's Special Services dataset.

§One value missing for the group of second-born children with no ASD code.

‖Case groups restricted to individuals diagnosed before 42 months of age or with an "ASD" code in the Education data who were approved for Special Needs Level 2 ("moderate ASD") or Level 3 ("severe to profound ASD") funding.

Table 2. Crude and adjusted odds ratios for the interpregnancy interval and autism spectrum disorder in second-born children from sibling pairs born in Manitoba to the same mother between January 1, 1988 and March 31, 2005, where no record of autism spectrum disorder was found for first-born siblings

Interpregnancy interval, months	Case Group 1*		Case Group 2†		Case Group 3‡	
	Crude OR (95% CI)	Adjusted§ OR (95% CI)	Crude OR (95% CI)	Adjusted§ OR (95% CI)	Crude OR (95% CI)	Adjusted§ OR (95% CI)
<12	1.07 (0.82–1.41)	1.22 (0.91–1.63)	1.19 (0.87–1.63)	1.36 (0.97–1.90)	1.49 (0.87–2.56)	1.72 (0.96–3.06)
12–23	0.94 (0.73–1.22)	1.08 (0.83–1.41)	1.04 (0.78–1.40)	1.19 (0.87–1.62)	1.42 (0.85–2.35)	1.59 (0.93–2.71)
24–35	0.98 (0.73–1.31)	1.08 (0.80–1.45)	1.01 (0.72–1.42)	1.10 (0.78–1.56)	1.13 (0.62–2.04)	1.29 (0.70–2.38)
≥36	1.00	1.00	1.00	1.00	1.00	1.00
p-value (test for linear trend)	–	0.20	–	0.07	–	0.05

OR: Odds ratio; CI: Confidence interval.

*At least one autism spectrum disorder (ASD) code in any of the following databases: Medical Services, Hospital Discharge Abstracts, Education, or Children's Special Services dataset.

†At least two ASD codes in one of the following databases: Medical Services, Hospital Discharge Abstracts, or Education; or at least one ASD code in two or more of the following databases: Medical Services, Hospital Discharge Abstracts, Education, or Children's Special Services dataset.

‡Record in the Children's Special Services dataset.

§Models adjusted for child's sex, mean-centered birth year, mean-centered birth year squared, intellectual disability (child), maternal age at delivery, and whether mother ever received income assistance.

change in the ORs for Case Groups 1 and 2 when all second-born children were included in the analysis, regardless of whether their mothers had experienced a pregnancy loss or termination after the birth of the older sibling (Sensitivity Analysis 1), while the effect sizes for both IPI categories increased and attained significance for Case Group 3. The ORs increased for intervals shorter than 12 months when the case groups were restricted to "more severe" cases (Figure 2, Sensitivity Analysis 2). The magnitude of that increase was greatest for Case Group 1 and negligible for Case Group 3.

While the overall tests of interaction were generally not significant, some of the stratum-specific associations were (see Supplementary Table).

DISCUSSION

Our discussion focuses on the findings for IPIs shorter than 12 months ("short IPIs"), as these were associated with an increased risk of autism in both the California[6] and the Norwegian[7] studies. (In contrast, significant associations for IPIs of 12–23 and 24–35 months were also reported in the former[6] but not the

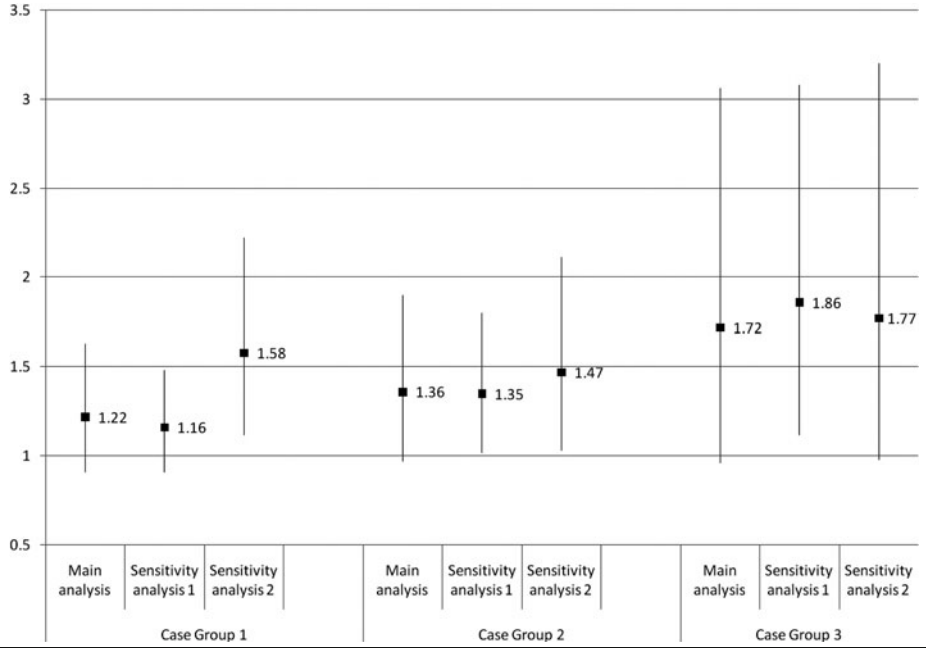

Figure 2. Results of sensitivity analyses (for interpregnancy intervals shorter than 12 months)
NOTE: The numbers shown in Figures 2 and 3 are odds ratios from logistic regression models, adjusted for child's sex, mean-centered birth year, mean-centered birth year squared, intellectual disability (child), maternal age at delivery, and whether the mother ever received income assistance. The bars represent 95% confidence intervals.
Case Group 1: At least one autism spectrum disorder (ASD) code in any of the following databases: Medical Services, Hospital Discharge Abstracts, Education, or Children's Special Services dataset.
Case Group 2: At least two ASD codes in one of the following databases: Medical Services, Hospital Discharge Abstracts, or Education; or at least one ASD code in two or more of the following databases: Medical Services, Hospital Discharge Abstracts, Education, or Children's Special Services dataset.
Case Group 3: Record in the Children's Special Services dataset.
Sensitivity Analysis 1: Includes second-born children from sibling pairs where a pregnancy loss or termination was reported between the older and younger siblings' births.
Sensitivity Analysis 2: Case groups restricted to individuals diagnosed before 42 months of age, or with an "ASD" code in the Education data and approved for Special Needs Level 2 ("moderate ASD") or Level 3 ("severe to profound ASD") funding.

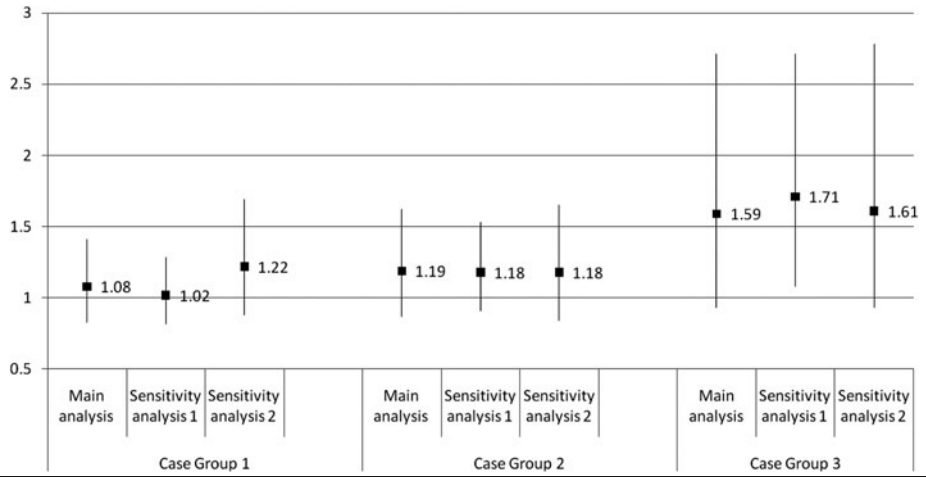

Figure 3. Results of sensitivity analyses (for interpregnancy intervals of 12–23 months)
See notes under Figure 2.

latter[7] study.) Despite the non-significant findings from the main analysis, our study does support an association between short IPIs and autism: when we restricted the case groups to "more severe" cases, the ORs increased and attained significance for Case Groups 1 and 2 (Figure 2, Sensitivity Analysis 2). While the ORs did not follow the expected pattern in this second sensitivity analysis (i.e., lowest in Case Group 1, highest in Case Group 3), the strongest effect was observed for Case Group 3

(OR = 1.77; 95% CI: 0.98–3.20), as predicted. The lack of a significant association for the latter group may have been due to its small number of cases (n = 132 for Sensitivity Analysis 2). Our a priori power calculations indicated we would have sufficient power to detect the ORs reported in the California study for IPIs shorter than 12 months, but those calculations were based on the estimated number of cases with at least one ASD code (i.e., Case Group 1).

The association between short IPIs and PDD-NOS and Asperger disorder combined was not significant in the Norwegian study.[7] The lower ORs for Case Groups 1 and 2 in the main analysis, compared to Case Group 3 (Table 2), could be attributable to a higher proportion of individuals on the milder end of the spectrum in those two groups, as evidenced by their lower proportions of "more severe" cases (Table 1). It is important to note, however, that higher proportions of false positives in those groups may also have attenuated the associations.

When the outcome was restricted to "more severe" cases versus no ASD (Figure 2, Sensitivity Analysis 2), the associations we observed more closely supported the findings from the Norwegian study,[7] where the ORs for autistic disorder were 1.71 (95% CI: 1.07–2.64) for intervals of 9–11 months and 2.18 (95% CI: 1.42–3.26) for intervals of less than 9 months. The association for short IPIs was stronger in the California study (OR = 3.39; 95% CI: 3.00–3.82).[6] The latter investigation reported significant heterogeneity in the IPI–autism association across maternal and paternal age strata, and stratified analyses by maternal race and use of California's Medicare system as payment for delivery yielded p-values approaching significance. To our knowledge, these factors were not considered in terms of potential effect modification in the Norwegian study.[7] However, the investigators did examine whether there was an interaction between maternal folate use and the IPI. They noted that, while not statistically significant, the effect of short IPIs was stronger in children whose mothers had not taken folic acid supplements prior to or during pregnancy (and that larger studies with more precise measures of folic acid intake are needed). If certain factors interact with the IPI, and those factors are distributed differently across study populations, it could explain some of the disparity in terms of the strength of the associations observed. Our study likely lacked sufficient power to detect significant interactions, but we conducted a supplementary analysis to provide preliminary data for those wishing to examine potential effect modifiers in future studies (see Supplementary Table).

Our study cohort was selected using hospital records and the Manitoba Health Insurance Registry. It should have captured most of the target population, as fewer than 1% of births in Manitoba take place in a non-hospital setting.[24] This, together with the fact that the health and education data capture information on almost all residents of Manitoba, means that our cohort was truly population-based. While this was a great strength of the study, we acknowledge the limitations imposed by the use of primarily administrative data to define the outcome of ASD, rather than "gold standard" case definitions based on developmental histories and observational assessments. We used three case groups to mitigate this limitation.

A further limitation was our inability to restrict the analysis to full-sibling pairs, as our dataset did not include information on paternity. A cohort of full-sibling pairs, where the older children do not have ASD, would provide greater assurance of minimizing any genetic contribution to ASD in the younger siblings. If some of the cases included in our analysis have an older paternal half-sibling with ASD, and if the IPIs for those second-born children tended to be longer, it may have attenuated the true effect of short IPIs on the risk of autism.

While the findings from three studies now support an association between short IPIs and autism, other questions remain. First, is the association stronger in certain groups, such as those defined by maternal age or ethnicity? Second, does folic acid intake prior to or during pregnancy modify the strength of the association? Third, are IPIs of 12 months or more also associated with an increased risk of autism, compared to longer IPIs (or some "ideal" interval)? Fourth, does the association persist in children from higher-parity births? The answers to these questions will help inform public health initiatives aimed at reducing the occurrence of autism.

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RÉSUMÉ

OBJECTIFS : Deux études ont fait état d'un risque accru de trouble autistique chez les enfants conçus moins de 12 mois après une naissance antérieure. Notre objectif était d'examiner l'association entre la période de non-gravidité (PNG) et les troubles du spectre de l'autisme (TSA) au sein d'une cohorte canadienne.

MÉTHODE : À l'aide de jeux de données administratives stockés au Centre de la politique des soins de santé du Manitoba, nous avons identifié des paires familiales composées du premier-né et du deuxième enfant (accouchements simples) nés entre 1988 et 2005. Les diagnostics de TSA ont été obtenus en interrogeant les demandes de paiement des médecins, les registres des sorties des hôpitaux, les données relatives à l'éducation et une base de données contenant de l'information sur les personnes identifiées pour un programme de surveillance des TSA mené au Manitoba entre 2002 et 2007. Des modèles de régression logistique ont été adaptés pour examiner l'association entre la PNG et les TSA chez 41 050 frères et sœurs second-nés dont le frère ou la sœur né(e) en premier n'avait pas de TSA, en utilisant une PNG de ≥ 36 mois comme catégorie de référence et en précisant trois groupes de cas. Le 1er groupe de cas incluait les personnes avec au moins un code de TSA (n = 490); le 2e groupe de cas incluait celles avec deux codes de TSA ou plus (n = 375); et le 3e groupe de cas comprenait les personnes ayant un dossier dans la base de données du programme de surveillance des TSA (n = 141).

RÉSULTATS : Le rapport de cotes (RC) ajusté pour les PNG de moins de 12 mois variait entre 1,22 (IC de 95 % : 0,91–1,63) pour le 1er groupe de cas à 1,72 (IC de 95 % : 0,96–3,06) pour le 3e groupe de cas. Lorsque les groupes de cas étaient limités aux personnes ayant un TSA grave, le RC augmentait, et il était significatif pour les 1er et 2e groupes de cas.

CONCLUSION : Nos constatations confirment également une association entre les PNG brèves et les TSA plus graves.

MOTS CLÉS : autisme; période de non-gravidité; analyse secondaire; données administratives; couplage des dossiers; Centre de la politique des soins de santé du Manitoba