Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada

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Abstract

Objective: To determine whether certain maternal characteristics and obstetric complications are associated with increased risk of autism spectrum disorders (ASD) in children.

Methods: Provincial delivery records identified the cohort of 218 890 singleton live births in Alberta, Canada, between January 1, 1998, and December 31, 2004. These were followed-up for ASD via ICD-9 diagnostic codes assigned by physician billing until March 31, 2008. Maternal and obstetric risk factors were also extracted from PDR.

Results: Prevalence and incidence of ASD in Alberta are in line with those reported elsewhere and suggest recent increases in rate of diagnosis and/or incidence. Boys have 5-fold higher prevalence than girls. The peak age of diagnosis occurs at age 3 years. Relative risk modelling indicates that the risk of ASD is elevated among children of older mothers and those who experience specific pregnancy and birth complications.

Conclusion: Certain maternal characteristics and obstetric complications are associated with ASD in children. We identified lower rates of ASD and later age at diagnosis among children of Aboriginal mothers that requires further research.

Keywords: *autism spectrum disorders, epidemiology, cohort studies, Alberta*

Introduction

The autism spectrum disorders (ASD) are a group of neurodevelopmental conditions that typically manifest before 3 years of age and are associated with impaired verbal and non-verbal communication and social interaction, and restricted and repetitive patterns of behaviour.[1] ASD reduces quality of life in affected children and their parents, and leads to extraordinary economic costs for society.[2] There have been relatively few population-based studies of ASD prevalence in Canada. A 2006 Montreal-based study of 27 749 children born between 1987 and 1998 suggests an ASD prevalence of 6.5 per 1000,[3] consistent with the prevalence estimates from the US and UK over the past several years;[4-7] estimates from service-based agencies in Manitoba and Prince Edward Island in 2002 put the prevalence among 5- to 9-year-olds at 3.8 to 4.1 per 1000;[8] and an educational database in British Columbia identifies the prevalence of ASD among 9-year-olds as 4.3 per 1000 in 2004.[9] (However, service-based databases are vulnerable to bias from diagnostic substitution.[9,10]) In general, there is a tendency for the prevalence of ASD to increase in more recent birth cohorts[7] and for diagnoses to be made at earlier ages. However, recent estimates from the US Centers of Disease Control and Prevention based on population-based data from 14 states place the median age of diagnosis at 4 to 5 years.[11]

The etiology of ASD is poorly understood, but genetic and environmental factors are believed to contribute. While some genetic risk factors are clearly established,[12] determining the contribution of the environment remains elusive. A recent review limited to only seven epidemiological studies suggests that advanced parental age, fetal growth restriction, and fetal or newborn hypoxia are associated with increased risk of developing ASD.[13] Based on the meta-analysis of 40 relevant studies, others concluded that, while it is premature to implicate specific pregnancy complications in the etiology of ASD, there is an excess of prenatal complications among children with ASD.[14]

Given the paucity of Canadian data on the epidemiology of ASD and the importance of replicating findings on maternal and obstetrics risk factors in large, representative and diverse populations,[13] our goals are (1) to estimate incidence and prevalence of ASD in a population-based birth cohort of residents in Alberta, Canada, and (2) to assess whether maternal characteristics and obstetric complications are associated with ASD in this population.

Methods

Record linkage

Delivery records held by the Alberta Perinatal Health Program (APHP) identified the

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cohort of singleton live births in the province of Alberta, Canada, between January 1, 1998, and December 31, 2004. The APHP provided information regarding relevant ante- and perinatal risk factors. Information on the risk factors was collected on admission to hospital for delivery, as part of routine clinical care. These are considered to be accurate and any internal inconsistency in the records is scrutinized by APHP; if an apparent error in the delivery records cannot be resolved, APHP records a missing value for a given variable. Maternal weight and height cut-offs were imposed by the data captured in the delivery records: actual values were not available to us.

The unique Personal Health Number of mother and child along with each child's gender and date of birth as recorded in each APHP file were used to follow-up the cohort through the records held by Alberta Health and Wellness (AHW). In the universal health care insurance system of Alberta, all residents are served by physicians and hospitals that bill the government for their services, with the fee linked to specific diagnostic codes from the *International Statistical Classification of Diseases and Related Health Problems, 9th revision* (ICD-9). Only children who were unambiguously matched in the APHP files to AHW records were followed-up by AHW until March 31, 2008, for (1) any of the two diagnostic codes listed with the physician billing record indicating ASD: ICD-9 codes 299.0, 299.8; (2) date of each ASD "service"; (3) specialty of the physician; (4) child's residency and mortality (in a given fiscal year ending on March 31) and (5) mothers' socioeconomic (SES) or Aboriginal status (available data did not allow us to distinguish Aboriginal mother from different economic statuses).

Study protocol was approved by the University of Alberta Health Ethics Research Board and the participating data custodians. Personal identifying data were not released to the investigators.

Statistical analyses

Four different case definitions were used in estimating the prevalence of ASD, which varied in stringency from "any claim by one physician" to "at least 2 ASD-linked billings from a pediatrician or psychiatrist." Incident cases of ASD were identified as the first physician service associated with an ASD diagnostic code (that is, the date of first filing was used as a proxy for age at diagnosis). Annual incidence was estimated separately for each sub-cohort defined by year of birth and gender. We recognize that this definition of incidence does not capture the true timing of the onset of ASD and hence, strictly speaking, our measure of incident case is rather akin to "recognized or diagnosed" case. Therefore, the notion of incidence (nearly impossible to estimate for psychiatric/chronic conditions from administrative data) is used in this paper with the above caveat in mind, accepting that it merely approximates true (un-measurable) incidence. After calculating crude ASD prevalence rate for strata of each risk factor, the relative risks (RR) and associated 95% confidence intervals (CI) were obtained in log-binomial regression that considered all covariates simultaneously. To reflect potential clustering of risk among children born to the same mother, we introduced random "mother effect" via generalized estimating equations assuming a compound symmetry covariance structure. We conducted a number of sensitivity analyses to explore the possible biases from outcome misclassification, uncontrolled confounding by parity, short follow-up for births after 2002, causal pathway from 1 to 5 minute Apgar scores, and uncertainty about causal pathway associated with cigarette smoking. All analyses were undertaken in SAS version 9.1 (SAS Institute, Cary, NC).

Results

There were 273 343 singleton live births in Alberta between 1998 and 2004. Of these, 25 970 children could not be unambiguously identified by AHW and 28 421 either died or lost residence during follow-up; a further 62 had missing gender, leaving 218 890 children for analysis of prevalence and incidence. The 28 421 children excluded from the study because of incomplete follow-up had similar distribution of all studied risk factors to those retained (details not shown).

The impact of varying case definitions on estimates of prevalence of ASD is illustrated in Table 1. The prevalence for both genders combined varied by a factor of 1.7, from 3 per 1000 (two services by any combination of psychiatrist or pediatrician) to 5.2 per 1000 (one claim by any physician). Regardless of the case definition, boys had approximately 5-fold higher prevalence than girls. Subsequent analyses first defined ASD based on "one claim by any physician," and were then repeated using the most stringent case definition. Estimate of prevalence were precise with standard errors in the order of 0.1 to 0.3 per 1000.

Time and gender trends in annual incidence show that peak age of diagnosis is between ages of 3 and 4 for both genders (Table 2). There was a 4- to 5-fold increase in annual incidence in more recent birth cohorts among 3-year-olds (0.52 per 1000 in 1998 to 2.32 per 1000 in 2004 for both genders). The patterns of results seen in Table 2 are also shown in Figure 1 for boys and Figure 2 for girls. There was an overall tendency for higher annual incidence among more recent birth cohorts across all age groups. Because the estimates of annual birth-cohort incidence were based on small numbers, each estimate was imprecise, with standard error of the rate as high as 70% to 100% of the rate estimate for younger ages (< 2 years) and females, decreasing to 10% to 20% for older age groups and more recent birth cohorts. All the numbers required to perform these calculations are presented in Table 2. Imprecision of these estimates precluded their further modelling, except that the effects of gender and birth cohort were examined in more detail below, after controlling for prenatal and perinatal factors (Table 4).

We examined trends by age of diagnosis, focusing on 1998 to 2002 birth cohorts (with at least 5 years of follow-up). Consistent with results shown in Table 2, both boys and girls were diagnosed at an earlier age, with median age of diagnosis 2 years earlier for boys and almost 3 years earlier for girls in 2002 compared to 1998 birth cohorts. Boys born in 1998 were diagnosed at a median (m) age of 69 months (inter-quartile range [IQR] 48-90), but girls

born in the same birth year were diagnosed at an older age (m = 74 months, IQR 40-104). In the 2002 birth cohort, on the other hand, both genders were diagnosed much younger (boys: m = 45, IQR 35-54; girls: m = 40, IQR 32-51). There was no indication of gender-by-birth-cohort interaction (details not shown).

Children who had missing information on maternal/obstetric covariates (n = 3673) were excluded from analyses of these risk factors. Excluded children were evenly distributed among birth years and had ASD rates similar to the rest of the cohort (16 cases, 4.4 per 1000). The maternal characteristics that were statistically associated with increased risk of ASD in a child included advanced maternal age (> 35 years versus ≤ 25 years: RR = 1.57, 95% CI = 1.25-1.97) with the bulk of excess risk in the women older than 25 (note: all groups with age greater than the reference category appeared to be at an increased risk); low maternal pre-pregnancy weight (RR = 2.15, 95% CI = 1.20-3.85); pre-pregnancy (not gestational) diabetes (RR = 1.65, 95% CI = 1.01-2.71); bleeding at less than 20 weeks of gestation (RR = 1.34, 95% CI = 1.08-1.67) and being nulliparous (Table 3).

Notably, children born to an Aboriginal mother appeared to have *reduced* rates of ASD (RR = 0.58, 95% CI = 0.40-0.84) and the median age at diagnosis was almost 2 years later than the rest of the cohort (m = 59.5 months, IQR 38-74 versus m = 36 months, IQR 47-65). Boys born to Aboriginal mothers (n = 26, m = 64.5 months, IQR 40-77) were diagnosed at much older age than girls (n = 8, m = 40 months, IQR 38-58). These numbers stand in stark contrast to ages of diagnoses of children born to mothers without any indications of SES disadvantage of marginalization ("Other" in Table 3): there is a much smaller overall differential in age of diagnosis among boys (n = 767, m = 47 months, IQR 37-66) and girls (n = 132, m = 44 months, IQR 32-62). Further, boys born to Aboriginal mothers appear to have been diagnosed on average 17 months later, while there does not appear to be a difference in age of diagnosis for Aboriginal and "other" girls.

TABLE 1
Prevalence of autism spectrum disorders[a] among Alberta singletons born 1998–2004

Case definition	Both genders N = 218 890		Male N = 111 960		Female N = 106 930	
	Count	Rate per 1000 (SE)[b]	Count	Rate per 1000 (SE)[b]	Count	Rate per 1000 (SE)[b]
One claim						
By any physician	1 138	5.2 (0.2)	952	8.5 (0.3)	186	1.7 (0.1)
By pediatrician or psychiatrist	1 016	4.6 (0.2)	849	7.6 (0.3)	167	1.6 (0.1)
Two claims						
By any physician	743	3.4 (0.1)	638	5.7 (0.2)	105	1.0 (0.1)
By psychiatrist or pediatrician	663	3.0 (0.1)	566	5.1 (0.2)	97	0.9 (0.1)

Abbreviations: N, overall sample size; SE, standard error.

[a] Relevant ICD-9 codes in any of the 3 diagnostic fields associated with physician billing, follow-up till March 31, 2008.

[b] Standard error of the rate calculated as $1000 \times (\text{rate}/1000)(1-\text{rate}/1000)/N)^{0.5}$.

Obstetric complications that significantly correlated with risk of ASD were pre-eclampsia (RR = 1.49, 95% CI = 1.00-2.23); breech or shoulder presentation in labour (RR = 1.31, 95% CI = 1.02-1.69); planned Caesarian section (RR = 1.23, 95% CI = 1.01-1.49); birth weight less than 2.5 kg (RR = 1.33, 95% CI = 1.01-1.75) and 1-minute Apgar of less than 7 (RR = 1.34, 95% CI = 1.15-1.55) (Table 4).

We conducted a number of sensitivity analyses. Using the most stringent ASD case definition and restricting the sample to nulliparous women (to correct for women altering their likelihood of having more children as a result of their firstborn being affected) and to 1998–2002 birth cohorts (ensuring longer follow-up) did not alter the pattern of results in Tables 3 and 4. Next, because Apgar score at 1 and 5 minutes post-partum are expected to be causally related, we examined the risk associated with trends in Apgar scores from 1 to 5 minutes. The excess risk was associated with low Apgar score at 1 minute, regardless of whether the score improved; the other risk estimates in Tables 3 and 4 did not change. Finally, smoking during pregnancy is an established risk factor for many of the covariates included in the multivariable regression model along with maternal smoking (e.g. low birth weight, prematurity, pre-eclampsia). Therefore, we restricted the analysis to children born to self-reported never-smokers (931 ASD cases, 169 372 births). The results are not materially different from those presented in Tables 3 and 4, except that among non-smokers there is a statistically significant excess of risk among larger women, that is, those with pre-pregnancy weight exceeded 91 kg (adjusted RR = 1.26, 95% CI = 1.01-1.57) and height equal to or over 152 cm (adjusted RR = 1.82, 95% CI = 1.02-3.23). There were too few observed ASD cases (191) to repeat the analysis only among children born to smokers. When risk factors that can be intermediate between smoking and ASD risk (low birth weight, prematurity, pre-eclampsia) were removed from the analyses, the estimated effect of smoking was unchanged.

Discussion

The prevalence and incidence of ASD in the birth cohort of children born in Alberta in 1998–2004 is in line with that observed in other jurisdictions. Not surprisingly, absolute rates of ASD vary by criteria used for case identification. However, time trends and associations with obstetric risk factors were robust to the ASD case definition. Our results also confirm that the risk of ASD is elevated among children of older mothers and those who experience complicated pregnancy and birth. Importantly, we identified lower rates of ASD and diagnosis

TABLE 2

Number of autism spectrum disorder cases[a] and incidence rate[b] by year of birth, age of diagnosis and gender among singletons born in Alberta, 1998–2004, followed up till March 31, 2008

Age (years)[c]		1		2		3		4		5		6		7		8		9	
Year of birth	Cohort size	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000	n	Rate per 1000
Both genders																			
1998	28 953	3	0.10	4	0.14	15	0.52	37	1.28	21	0.73	22	0.76	24	0.83	21	0.73	27	0.94
1999	29 466	4	0.14	9	0.31	29	0.98	34	1.16	29	0.99	33	1.12	21	0.72	36	1.23		
2000	29 222	1	0.03	22	0.75	28	0.96	40	1.37	32	1.10	22	0.76	29	1.00				
2001	30 127	2	0.07	11	0.37	46	1.53	40	1.33	29	0.97	35	1.17						
2002	31 775	1	0.03	21	0.66	52	1.64	48	1.51	51	1.61								
2003	33 917	2	0.06	31	0.91	54	1.59	59	1.74										
2004	35 430	3	0.08	28	0.79	82	2.32												
TOTAL	218 890	16	0.07	126	0.58	306	1.40	258	1.18	162	0.74	112	0.51	74	0.34	57	0.26	27	0.12
Males																			
1998	14 874	1	0.07	2	0.13	14	0.94	34	2.29	21	1.42	19	1.28	23	1.56	18	1.22	21	1.42
1999	15 059	3	0.20	8	0.53	25	1.66	27	1.80	26	1.73	23	1.54	20	1.34	31	2.08		
2000	14 858	1	0.07	17	1.14	25	1.68	36	2.43	29	1.96	20	1.36	24	1.63				
2001	15 489	2	0.13	10	0.65	36	2.33	37	2.40	22	1.43	32	2.08						
2002	16 224	0	0.00	15	0.92	39	2.41	38	2.35	41	2.54								
2003	17 325	1	0.06	22	1.27	47	2.72	52	3.01										
2004	18 131	3	0.17	17	0.94	70	3.87												
TOTAL	111 960	11	0.10	91	0.81	256	2.29	224	2.01	139	1.25	94	0.85	67	0.60	49	0.44	21	0.19
Females																			
1998	14 079	2	0.14	2	0.14	1	0.07	3	0.21	7	0.50	3	0.21	1	0.07	3	0.21	6	0.43
1999	14 407	1	0.07	1	0.07	4	0.28	3	0.21	3	0.21	10	0.69	1	0.07	5	0.35		
2000	14 364	0	0.00	5	0.35	1	0.07	4	0.28	3	0.21	2	0.14	5	0.35				
2001	14 638	0	0.00	0	0.00	10	0.68	3	0.21	7	0.48	5	0.34						
2002	15 551	1	0.06	6	0.39	13	0.84	10	0.64	9	0.58								
2003	16 592	1	0.06	9	0.54	7	0.42	8	0.48										
2004	17 299	0	0.00	11	0.64	10	0.58												
TOTAL	106 930	5	0.05	34	0.32	46	0.43	31	0.29	29	0.27	20	0.19	7	0.07	8	0.07	6	0.06

Abbreviations: n, number.

[a] Number of autism spectrum disorder cases, using one physician claim rule.

[b] Per 1000 members of the birth cohort (prevalent cases excluded from denominator).

[c] Approximated by year of diagnosis since birth.

FIGURE 1
Rate of autism spectrum disorders per 1000 in males by birth cohorts (1998–2004) in Alberta

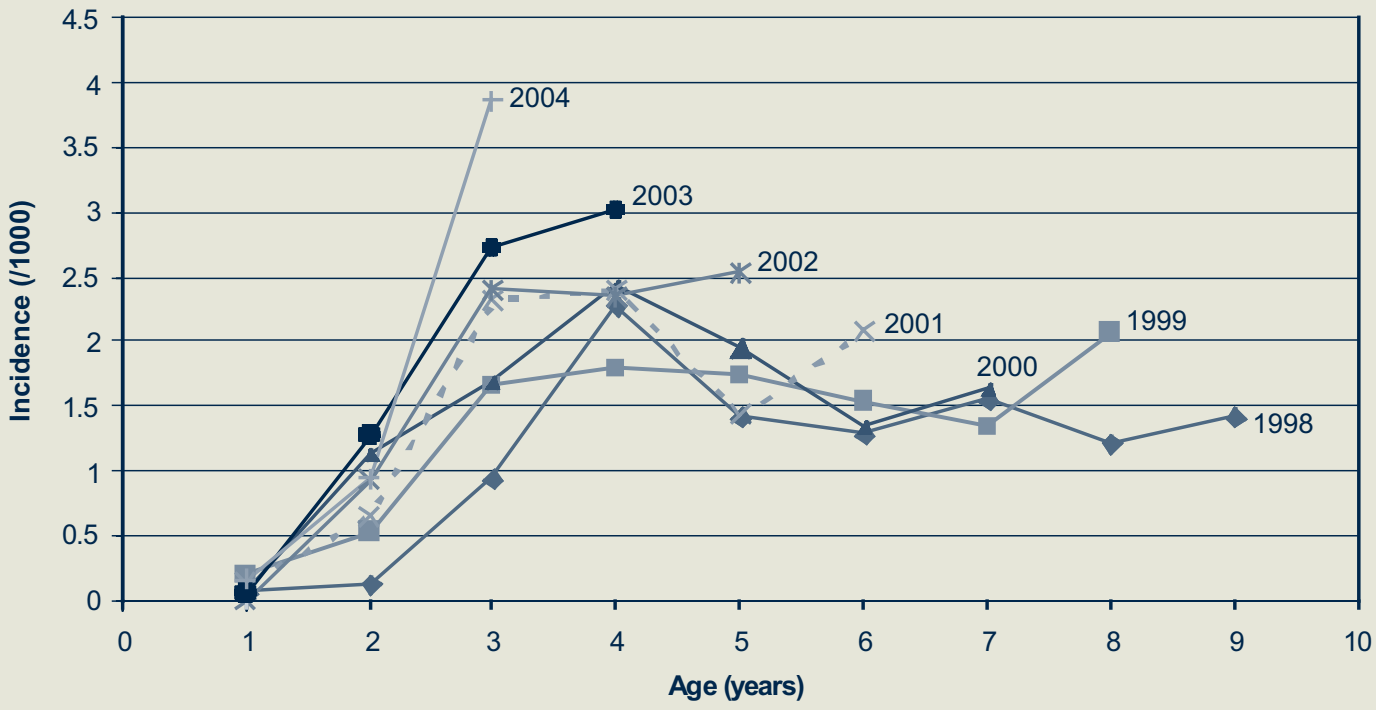

FIGURE 2
Rate of autism spectrum disorders per 1000 in females by birth cohorts (1998–2004) in Alberta

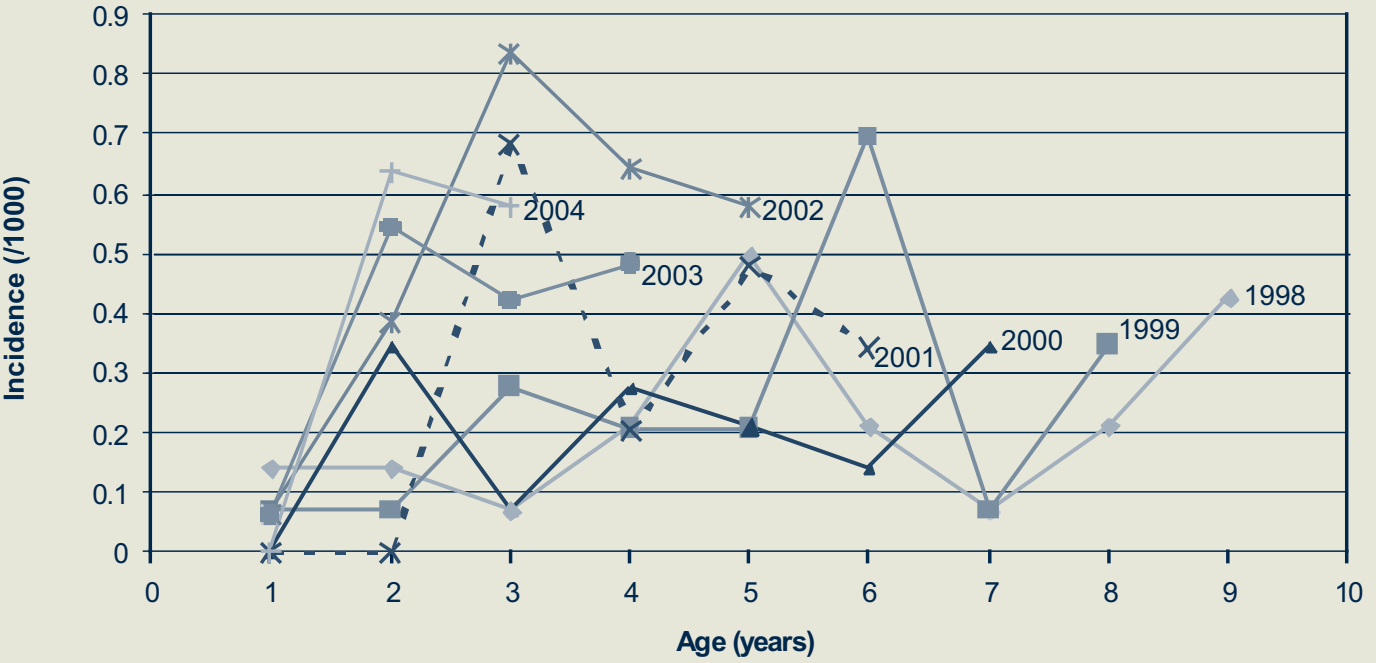

TABLE 3

Autism spectrum disorders and ante- or perinatal risk factors among singleton live births in Alberta, 1998–2004 (relative risk model spans Tables 3 and 4)

Risk factor		Number of ASD cases	Number of singleton live births	Crude rate (per 1000)[a]	RR[b]	95% CI
Maternal age (years)	≤ 25	276	66 736	4.1	1.00	—
	25 ≤ 30	372	70 256	5.3	1.31	1.11 - 1.56
	30 ≤ 35	339	56 369	6.0	1.51	1.26 - 1.80
	> 35	149	24 573	6.1	1.57	1.25 - 1.97
	Unknown	2	956	2.1	0.56	0.14 - 2.27
Maternal weight > 91 kg	Yes	109	17 417	6.3	1.18	0.96 - 1.44
	No	1013	197 800	5.1	1.00	—
	Unknown	16	3673	4.4	[c]	
Maternal weight < 45 kg	Yes	11	1097	10.0	2.15	1.20 - 3.85
	No	1111	214 120	5.2	1.00	—
	Unknown	16	3673	4.4	[c]	
Maternal height < 152 cm	Yes	16	3941	4.1	0.64	0.39 - 1.05
	No	1106	211 279	5.2	1.0	—
	Unknown	16	3670	4.4	[c]	
Pre-pregnancy diabetes	Yes	16	1645	9.7	1.65	1.01 - 2.71
	No	1106	213 575	5.2	1.00	—
	Unknown	16	3670	4.4	[c]	
Gestational diabetes	Yes	54	7453	7.2	1.24	0.94 - 1.65
	No	1068	207 767	5.1	1.00	—
	Unknown	16	3670	4.4	[c]	
Bleeding < 20 weeks	Yes	90	12 323	7.3	1.34	1.08 - 1.67
	No	1032	202 897	5.1	1.00	—
	Unknown	16	3670	4.4	[c]	
Bleeding ≥ 20 weeks	Yes	45	7046	6.4	1.05	0.78 - 1.43
	No	1077	208 174	5.2	1.00	—
	Unknown	16	3670	4.4	[c]	
Cigarette smoking (any)	Yes	191	45 846	4.2	0.86	0.72 - 1.02
	No	931	169 374	5.5	1.00	—
	Unknown	16	3670	4.4	[c]	
Poor weight gain (26-36 weeks < 0.5 kg/week)	Yes	15	3095	4.8	0.95	0.57 - 1.59
	No	1107	212 125	5.2	1.00	—
	Unknown	16	3670	4.4	[c]	
Parity	0	535	90 431	5.9	1.00	—
	1	416	75 519	5.5	0.91	0.79 - 1.04
	2	119	31 962	3.7	0.61	0.49 - 0.76
	3	39	11 493	3.4	0.54	0.38 - 0.75
	≥ 4	24	8174	2.9	0.50	0.32 - 0.76
	Unknown	5	1311	3.8	0.79	0.33 - 1.92
Socio-economic status of mother	Aboriginal group[d]	34	14 486	2.3	0.58	0.40 - 0.84
	Low income[e]	149	28 605	5.2	1.12	0.93 - 1.34
	Welfare	41	7601	5.4	1.26	0.91 - 1.75
	Other	899	164 940	5.5	1.00	—
	Unknown	15	3258	4.6	0.88	0.80 - 0.97

Abbreviations: CI, confidence interval; N, overall sample size; n, subsample size; RR, relative risk.

[a] N = 218 890.

[b] n = 215 217; adjuster relative risks (RR) for factors in Tables 3 and 4 and 95% confidence intervals (CI), corrected for clustering of births with mother.

[c] 3673 subjects excluded from the RR model because of missing covariates (see text for details).

[d] Treaty Aboriginal status, qualifying for subsidies from the federal government regardless of family income.

[e] Completely or partially subsidized health insurance premiums.

TABLE 4

Autism spectrum disorders and at-birth or delivery risk factors, child's gender and birth year among singleton live births in Alberta, 1998–2004 (relative risk model spans Tables 3 and 4)

Risk factor		Number of ASD cases	Number of singleton live births	Crude rate (per 1000)[a]	RR[b]	95% CI
Pre-eclampsia	Yes	27	2747	9.8	1.49	1.00 - 2.23
	No	1095	212 473	5.2	1.00	—
	Unknown	16	3670	4.4		
Presentation	Cephalic	1049	206 590	5.1	1.00	—
	Breech/Shoulder	79	10 557	7.5	1.31	1.02 - 1.69
	Unknown/Other	10	1743	5.7	1.22	0.63 - 2.35
Type of labour	Spontaneous	597	123 434	4.8	1.00	
	Induced	337	60 930	5.5	1.07	0.93 - 1.23
	No labour[3,c]	149	22 185	6.7	1.23	1.01 - 1.49
	Unknown	55	12 341	4.5	0.79	0.57 - 1.08
Delivery by Caesarian section	Yes	304	49 152	6.2	1.04	0.88 - 1.22
	No	834	169 738	4.9	1.00	—
Gestational age	< 37 weeks	125	17 889	7.0	0.97	0.75 - 1.25
	≥ 37 weeks	1011	200 557	5.0	1.00	—
	Unknown	2	444	4.5	0.94	0.24 - 3.72
Birth weight (kg)	< 2.5	100	13 130	7.6	1.33	1.01 - 1.75
	2.5-4.5	1012	201 598	5.0	1.00	—
	> 4.5	26	4125	6.3	1.00	0.67 - 1.49
	Unknown	0	37	0.0		
Apgar at 1 min	< 7	248	34 275	7.2	1.34	1.15 - 1.55
	7-10	888	184 301	4.8	1.00	—
	Unknown	2	314	6.4	2.08	0.53 - 8.26
Apgar at 5 min	< 7	34	4094	8.3	1.03	0.71 - 1.49
	7-10	1107	214 795	5.2	1.00	—
Female child		186	106 930	1.7	0.20	0.17 - 0.24
Birth year	1998	174	28 953	6.0	1.95	1.53 - 2.47
	1999	195	29 466	6.6	2.09	1.65 - 2.63
	2000	173	29 222	5.9	1.89	1.49 - 2.39
	2001	164	30 127	5.4	1.69	1.33 - 2.15
	2002	172	31 775	5.4	1.69	1.33 - 2.14
	2003	146	33 917	4.3	1.32	1.04 - 1.69
	2004	114	35 430	3.2	1.00	—

Abbreviations: CI, confidence interval; N, overall sample size; n, subsample size; RR, relative risk.

[a] N = 218 890.

[b] n = 215 217; adjuster relative risks (RR) for factors in Tables 3 and 4 and 95% confidence intervals corrected for clustering of births with mother.

[c] Caesarian-section delivery without labour (likely planned Caesarian section; other Caesarian section deliveries may have been preceded by spontaneous or induced labour).

at later age among children of Aboriginal mothers, which, to our knowledge, has not previously been reported. It should be noted that our results were obtained in the context of the health care system that exists in the Canadian province of Alberta and our findings may reflect peculiarities to this context (especially trends in time period and age at diagnosis, as well as the SES gradients).

Our study is one of the few epidemiological studies of pre- and perinatal risk factors for ASD that meet the stringent quality criteria of Kolevzon et al.,[13] namely, a large and well-defined population-based sample with prospective standardized risk factors and outcome assessments. Among studies addressing association of ASD with pre- and perinatal factors, ours is the second largest study in terms of number of ASD cases, after Croen et al.,[15] and is among the first Canadian reports.[16] Consistent with previous literature, we observed that risk of ASD was related to increased maternal age and obstetric complications. We observed that low birth weight, but not preterm birth (gestational age < 37 weeks), was associated with risk of ASD. Other studies, which have used non-standard definitions of prematurity (ranging from less than 28 to 35 weeks of gestation), have reported varying evidence of association with ASD.[17-19] Preliminary analysis suggests that the relationship between gestational age and risk of ASD is not straightforward in the Alberta birth cohort, with some evidence that more severely premature births are associated with higher risk of ASD. We will examine the relationship between gestational age and birth weight (across the continuum) and risk of ASD in a future study. We replicated the well-known gender difference in ASD risk.[20] Our study did not confirm association of ASD with maternal smoking, although the association was reported with daily, not ever-smokers in pregnancy.[21] Our work adds evidence in support of association of ASD with breech presentation,[17] pre-pregnancy diabetes[21,22] and pre-eclampsia.[17] However, it should be noted that Gardener et al.[14] observed that the effect of pre-eclampsia on risk of ASD meta-analysis was heterogeneous among studies, concluding that it is unlikely that it is associated with risk of ASD.

A novel finding, which should be treated with caution, is elevated risk among children of mothers with lower pre-pregnancy weight. In this regard, it is noteworthy that Wentz et al.[23] reported excess of ASD among patients with severe eating disorders. If it were true that such conditions have a genetic component, then low pre-pregnancy weight of the ASD case's mother may simply be a marker for a genetic risk factor common to both eating disorders and ASD. The observation that among non-smoking mothers the risk of ASD in children was confined to those with greater weight and height is new but congruent with a previous report.[16] It must be noted that these associations with crude anthropometric measures can be the result of confounding by racial differences (and the underlying genetics) or differences in nutritional habits/acculturation.

The most significant and unexpected association is that of reduced rates and later diagnosis of ASD among children, especially boys, of Aboriginal mothers. It may point to poor access to diagnostic and treatment facilities in remote areas (note that children of mothers who were on welfare—perhaps similarly economically disadvantaged, but more likely to reside in urban areas—were not at increased risk), but a difference in genetic vulnerability cannot be ruled out. A two-fold increase in ASD risk was previously associated with urbanization (regarding place of birth) in Denmark;[24] therefore, if it were true that rural/reserve lifestyle is protective for ASD, then our observation of protective effect of having an Aboriginal mother may also reflect the associated level of "urbanization." Shattuck et al.[25] observed that the nature or trajectory of ASD can affect age of diagnosis, which suggests that our observation of later diagnosis among boys born to Aboriginal mothers may be attributed to variation in the course of the disease in this sub-population compared to the rest of the population. Close scrutiny of ASD trajectory (the nature and age of onset of specific symptoms), not feasible within the context of this study, is needed to address this possibility. It would also be important to determine whether children born to Aboriginal mothers are also diagnosed with other psychiatric disorders at a later age to check whether our findings are specific to ASD. Our findings are generally in agreement with those of Leonard et al.[22] who reported decreased risk of autism with mental retardation among Australian Aboriginal children relative to Caucasians, pointing out to apparent differences in risk of ASD among Aboriginal people living in industrialized countries compared to the rest of the population.

There is no uniform ASD case ascertainment methodology in the health care system of Alberta. Because of universal health care in Canada, most children and families have a community physician who provides primary health care. In Alberta, there is no systematic screening for ASD, although a universal community health centre visit for vaccination at age 18 months and 4 to 5 years includes developmental surveillance. In general, ASD diagnosis is provided by a specialized multi-disciplinary team at a small number of regional developmental assessment centers. However, for some children, a community pediatrician may be the first to diagnose ASD and record this in the billing records. A detailed analysis of access to specialized assessment services is beyond the scope of this paper, but is certainly of interest, particularly given that our results suggest that it may be different for different SES or ethnic groups (e.g. Aboriginal families).

According to Shattuck et al., boys tend to be diagnosed with ASD at a younger age than girls,[25] which is supported by our data in the older (e.g. 1998) but not the younger (e.g. 2002) birth cohorts. The more recent birth cohorts showed either no difference in age of diagnosis by gender or a slightly younger age of diagnosis among girls. This difference in patterns of diagnosis can be attributed either to real changes in diagnostic practices over time and between US and Alberta, or differences in information on ASD diagnosis between our studies. Shattuck et al.[25] used both health (broadly defined) and educational records, while we were limited to diagnoses made by physicians. Therefore, Shattuck et al.[25] were likely to miss fewer cases and perhaps had their sample enriched by cases with less severe or pronounced disease trajectory, which would also account for later

expected age of diagnosis—5 years versus 3 to 4 years in our cohorts. Differences in our studies can also be attributed to more complete case ascertainment by Shattuck et al.[25] as witnessed by the high prevalence observed in their work.

The most obvious shortcoming of our work is lack of independent verification of ASD diagnosis by direct clinical assessment using gold standard measures, which would certainly affect estimates of incidence and prevalence. However, it appears that risk factor profiles are independent of variation in the case definitions considered here, thus our main conclusions appear to be robust to diagnostic misclassification. The case ascertainment method most comparable to our methodology (one physician claim) had reasonable sensitivity (59.7%) and specificity (85.2%) in another Canadian province and was not materially inferior to the diagnostic rule that also considered outpatient databases and/or multiple physician claims; both measures were independent of risk factors (e.g. gender).[26] Data from the Alberta delivery records on risk factors may have contained errors, but these would be independent of outcome definition, resulting in attenuation of risk estimates.[27] The available data did not allow us to consider either presence of birth defects or fathers' age (an established risk factor[13]). It should be noted that maternal and paternal age both appear to contribute to risk of ASD independently.[28,29] We were not able to explicitly control for genetic risk factors[12] beyond modelling correlation in risk of ASD due to clustering of children within their mother.

In conclusion, we confirmed in a large population-based study that maternal characteristics and obstetric complications are associated with the risk of ASD in the Canadian province of Alberta. We obtained the first estimates of prevalence and incidence of ASD in Alberta that are in line with those reported in other jurisdictions and suggest recent increases in the rate of diagnosis and/or incidence. The *apparently* reduced risk of ASD in Aboriginal populations requires further research. Although our epidemiological ASD definition appears to be useful, it has to be validated to provide more precise picture of burden of ASD, not just to detect trends. Population-level surveillance to monitor trends in ASD with adjustment for diagnostic biases and with special focus on socio-economically marginalized and rural populations remains a priority for public health research. Accurate estimates of ASD rates are essential to health service planning for the many individuals and families affected by ASD, and understanding its antecedents at a population-level may provide important new insights into the etiology of ASD.

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