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Intergenerational Effects Of Adverse Birth Outcomes Of Parents And Offspring Autism Spectrum Disorder (asd) Risk In Denmark: A Population-Based Cohort Study

Jingyuan Xiao
jingyuan1208@gmail.com

Intergenerational Effect of Adverse Birth Outcomes of Parents and Offspring Autism Spectrum Disorder (ASD) risk in Denmark: A Population-based Cohort Study

Jingyuan Xiao

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Yale School of Public Health

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Thesis Advisor: Zeyan Liew, PhD, MPH

Second Reader: Yawei Zhang, MD, PhD, MPH

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Abstract

Introduction: Animal studies have suggested that exposure-induced epigenetic reprogramming of the germlines affects neurodevelopmental outcomes in the next generation, but possible transgenerational effects of parental adverse birth outcomes and offspring autism spectrum disorder (ASD) risk have not been studied in humans.

Objective: To evaluate whether parents being born preterm or low birth weight were associated with risks for ASD in their offspring.

Methods: We conducted a Danish population-based cohort study including mothers and fathers born since 1978 who also have had an offspring registered in Denmark during 1990-2013. Information on gestational age and birth weight were recorded in the Danish Medical Birth Register; ASD diagnoses of the offspring were ascertained using records from the Danish Central Psychiatric Registry. We identified 235,228 mother-child pairs and 161,606 father-child pairs for statistical analyses. We estimated Odds Ratio (OR) and 95% confidence intervals (CI) for ASD according to parental preterm and low birth weight status, with or without adjustment for grand-maternal sociodemographic factors including age, parity and education level.

Results: Of all parents included in the study, 5.4% mothers (12,749) and 4.4 % fathers (7,084) had low birth weight, and approximately 4.0% mothers (9,724) and fathers (7,413) were born preterm. Children of mothers with adverse birth outcomes had about 20% higher risk for ASD (low birth weight, OR=1.19, 95% CI: 1.03-1.38; preterm birth, OR=1.19, 95% CI= 1.01-1.40), compared with mothers born with normal birth weight or born at term. Paternal adverse birth outcomes were also associated with about 30% elevated risks for ASD in the offspring (low birth weight, OR=1.31, 95% CI= 1.07, 1.59; preterm birth, OR=1.29, 95% CI=1.06, 1.57). These associations were slightly attenuated upon adjustment for grandmaternal sociodemographic factors.

Conclusions: Offspring of parents born with adverse outcomes showed slightly elevated risks for ASD. Several etiological pathways could potentially explain this association, including that adverse birth outcomes in parents might act as a proxy indicating complications or harmful in utero exposures that had affected the germlines of the parents, or that parents born disadvantaged also had poorer physical health and lower socioeconomic achievement persisted into adulthood, and that these mechanisms in combined influencing disease risks in their offspring.

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1. Introduction

Autism spectrum disorder (ASD), a heterogeneous group of neurodevelopmental disorders, is characterized by a range of social impairments and behavioral difficulties. The estimated prevalence of ASD is more than 1.5% in developed countries, and ASD diagnoses among more recent cohorts are still on the rise.[1,2] ASD has long been linked to high individual and community economic burdens,[1] as well as substantial global health consequences.[3] A wide number of genetic[4–6] and environmental risk factors[7–9] for developing ASD have been identified. Over the last decade, epigenetic studies provided additional insight into plausible mechanisms through which health-related characteristics of adults might play a role in the long-term neurodevelopment of their offspring. For instance, studies have suggested that advanced maternal and paternal age might contribute to offspring ASD[10–13] by inducing germline *de novo* mutations[14,15] that occurred in children as a consequence of a variation in the parent's egg or sperm cell.[16]

The intergenerational effects of parents' early life experiences specifically on offspring ASD risk have not been extensively studied, primarily due to the lack of high-quality prospective data. Nevertheless, evidence regarding transgenerational inheritance of a range of disease risks is accumulating in recent literature. Studies have shown associations between *in utero* exposures to diethylstilbestrol[17–20] and smoking[21–23] in women, and general adverse health conditions in the following generation, such as birth defects,[18–20] menstrual irregularities,[17]and childhood asthma.[21–23] Similar associations of harmful gestational exposures to environmental agents influencing the well-being of the next generation have been observed on the father's side.[24,25] A few studies have examined such effects in the context of neurodevelopment. Maternal exposure to diethylstilbestrol has been linked to attention-deficit/hyperactivity Disorder (ADHD), possibly through mechanisms involving epigenetic alterations.[26] Narrowing the focus to ASD, a Swedish study on advancing

grandparental age has indicated that the risk for ASD could develop across successive generations.[27] Additionally, prenatal exposure to nicotine in women has been associated with increased offspring ASD risk and autistic traits.[28]

In this framework, the specific role of adverse parental birth outcomes in the development of offspring ASD has remained unexplored. Nonetheless, preterm birth[29,30] and low birth weight[9] in children have been well-established risk factors for ASD. Existing evidence on children's own birth characteristics provides two plausible mechanisms for the transmission of these effects to the following generation. One of these two mechanisms is based on possible associations between poor birth outcomes and extrinsic disadvantageous conditions that persist across generations.[31] Unfavorable outcomes at birth, in turn, might result in further negative effects, such as worse overall health, social difficulties, and poorer socioeconomic achievement in adulthood.[32–34] Further along the trajectory, these characteristics of parents could potentially lead to elevated ASD risk in the next generation. The other mechanism involves possible germline alterations passing on to future generations as a result of parental exposures to environmental risks while in utero, which have been observed in both animal[35–37] and human studies.[38,39] Therefore, it is probable that adverse intrauterine experiences that lead to prematurity and reduced fetal growth resulting in subsequent *de novo* mutations that could be passed down to the offspring. Adverse birth outcomes of parents might act as a proxy measure of effects of persistent sociodemographic disadvantages and harmful *in utero* exposures of the parents on ASD risks in their offspring.

In our attempt to evaluate the above hypothesized relationships, we conducted a record-linkage study using data from several birth and medical registries from Denmark starting in 1978 and investigated whether maternal and/or paternal adverse birth outcomes are associated with risk of ASD in their children.

2. Methods

2.1 Data Source and Study Population

The source population of this study consisted Danish individuals born since 1978 who also have had an offspring registered in Denmark during the year of 1990-2013. We accessed both the parent and child records from the Danish Medical Birth Register (DMBR), a national electronic data register established in 1973 that collects extensive information on pregnancy and birth outcomes across Denmark.[40] Parent-child pairs were linked using the unique 10-digit civil registration identifier assigned to all Danish residents and only singleton births were included. The DMBR only started to collect information on gestational age since 1978 thus mothers or fathers born between 1973-1977 were excluded. We relied on ICD-10 codes for ASD diagnoses registered in the medical records since 1990, and children needed to be at least 3 years of age by the end of study follow-up in 2016. Altogether, we identified 235,228 mother-child pairs and 161,606 father-child pairs with complete information regarding parental gestational age at birth and birth weights for statistical analyses.

2.2 Parental Birth Outcomes

Information on birth weight and gestational age for both the parents and the children were obtained from the DMBR. Low birth weight was defined according to the World Health Organization's standards as weight at birth less than 2,500 grams,[41] while preterm birth was referred to as less than 37 completed weeks of gestation.[42] We further classified neonates born prior to 32 completed weeks of gestation as very preterm births, and defined weighing less than normal but delivered at full term as term low birth weight. The information regarding gestational age recorded in the DMBR was mostly based on ultrasound examinations done before 24 weeks

of gestation conducted by midwives (~97%) with few calculated from the first day of the last menstrual period (LMP).

2.3 Autism Spectrum Disorders

We ascertained ASD diagnoses in children by linking DBMR to the Danish Psychiatric Central Registry, which included longitudinal information on all psychiatric hospital admissions since 1969.[43,44] Starting from 1995, outpatient visits in Denmark have been recorded as well.[43,44] All diagnoses were based on the International Classification of Diseases 10th Edition (ICD-10 F84.0, F84.1, F84.5, F84.8, and F84.9 for Autism Spectrum Disorder).

2.4 Statistical Analysis

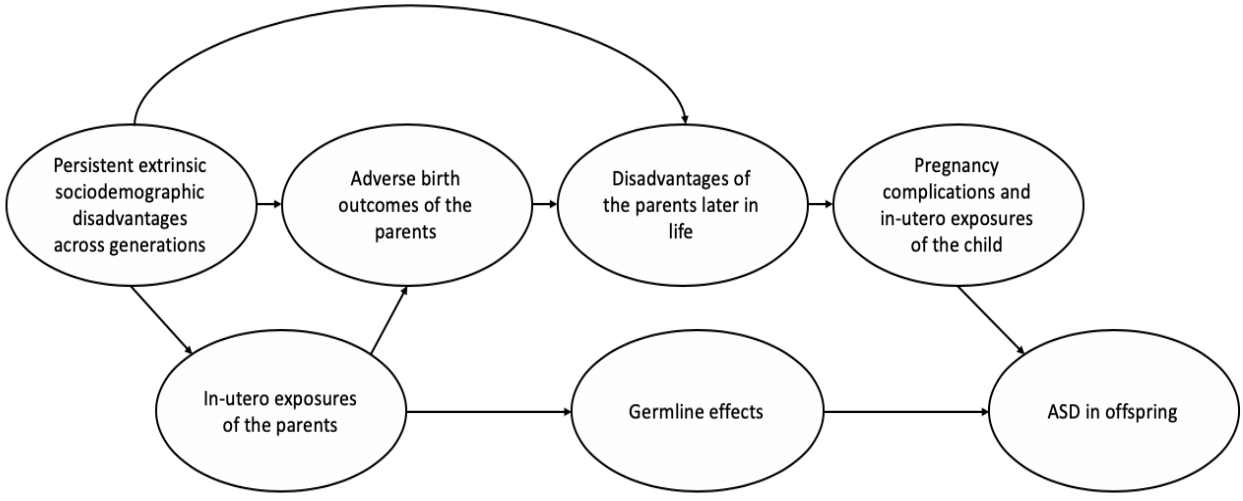
We used directed acyclic graphs (DAGs) to conceptualize possible causal relationships between parental adverse birth outcomes and offspring ASD (Figure 1). Poor birth outcomes of mothers and fathers were used as a proxy to indicate adverse intrauterine exposures and persistent sociodemographic disadvantages. Heritable effects of these harmful environmental exposures may then lead to offspring ASD through two plausible pathways, 1) epigenetic modifications in the germ cell; 2) lifelong disadvantages in parents mediated via harmful intrauterine exposures in offspring (Figure 1). To test our hypotheses, we conducted logistic regression analyses with predefined categories of birth outcomes as exposure variables and with ASD diagnosis as the outcome variable.

We first estimated the crude association between maternal and paternal birth outcomes and offspring ASD. Next, we constructed two adjusted models including covariates data obtained from the DMBR. The first model adjusted for year of birth of the parents [1978-1982, 1983-1987, 1988-1992, 1993-2001] and place of residence at birth in Denmark (Copenhagen, its suburbs [Aarhus, Odense, Aalborg], and other cities/towns), and the second additionally included grandmaternal

parity (number of previous births), grandmaternal education level (primary and lower secondary, upper secondary education and academy profession degree, bachelor and above), and grandmaternal age at the time of delivery (<25, 25–29, 30–34, 35–39, >40). Missing values were treated as a separate category.

Further analyses stratified by offspring sex to test for potential sex-specific associations were performed. Analyses restricted to first born children only, children diagnosed with autistic disorder (code F84.0), and parents born at full term were also conducted. We additionally compared the risk of ASD between parents born very preterm (<32 gestational weeks) to those born at full term and with normal weight. In the next step, we estimated the effects of one parent's adverse birth outcomes controlling for the other parent. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Figure 1. Direct acyclic graph of the possible relationships between adverse birth outcomes of the parents and ASD in the offspring.



3. Results

Sociodemographic and pregnancy-related characteristics of mothers and fathers by ASD status of the offspring are presented in Table 1. Overall, ASD cases were more often descendants of less educated grandmothers, born to grandmothers with young (<25) and advanced maternal age (>=40), and if the grandmothers were living in Copenhagen. Parents of children with and without ASD were of similar grandmother's parity.

Table 1. Sociodemographic characteristics of study population by offspring ASD status

Demographic and pregnancy characteristics		ASD cases		Noncases	
		n	%	n	%
Mother (n=235,228)					
	Year of Birth				
	1978 - 1982	2,015	65.64	135,942	58.56
	1983 - 1987	857	27.92	74,428	32.06
	1988 - 1992	194	6.32	20,153	8.68
	1993 - 2001	na	0.13	1,635	0.70
	Grandmaternal Education Level				
	Primary and Low Secondary	1,793	58.40	117,598	50.65
	Upper Secondary and Academy Profession	922	30.03	79,088	34.07
	Bachelor+	316	10.29	32,557	14.02
	Grandmaternal Parity				
	1	1,415	46.09	105,115	45.28
	2	1,068	34.79	84,164	36.25
	3	587	19.12	42,879	18.47
	Grandmaternal Residence at Birth				
	Copenhagen	399	13.00	18,793	8.09
	Aarhus, Odense, or Aalborg	305	9.93	26,847	11.56
	Others	2,366	77.07	186,518	80.34
	Grandmaternal Age at Delivery				
	<25	1,521	49.54	98,028	42.00
	25 - 29	946	30.81	84,821	36.54
	30 - 34	430	14.01	37,465	16.14
	35 - 39	153	4.98	10,429	4.49
	>39	20	0.65	1,415	0.61
Father (n=161,606)					
	Year of Birth				
	1978 - 1982	1,306	70.22	103,506	64.79
	1983 - 1987	452	24.30	46,273	28.97
	1988 - 1992	98	5.27	9,433	5.90
	1993 - 2001	4	0.22	534	0.33
	Grandmaternal Education Level				
	Primary and Low Secondary	1,013	54.46	77,464	48.49
	Upper Secondary and Academy Profession	618	33.23	55,550	34.77
	Bachelor+	198	10.65	24,815	15.53
	Grandmaternal Parity				
	1	802	43.12	71,257	44.61
	2	707	38.01	59,612	37.32
	3	351	18.87	28,877	18.08
	Grandmaternal Residence at Birth				
	Copenhagen	220	11.83	12,972	8.12
	Aarhus, Odense, or Aalborg	160	8.60	18,456	11.55
	Others	1,480	79.57	128,318	80.33
	Grandmaternal Age at Birth				
	<25	822	44.19	65,253	40.85
	25 - 29	630	33.87	59,216	37.07
	30 - 34	299	16.08	27,020	16.91
	35 - 39	94	5.05	7,230	4.53
	>39	15	0.81	1,027	0.64

Of all parents included in the final analyses, 5.4% mothers (12,749) and 4.4 % fathers (7,084) had low birth weight, and approximately 4.0% mothers (9,724) and fathers (7,413) were born preterm.

Table 2 below presents unadjusted and adjusted odds ratios of adverse parental birth outcomes with respect to diagnosis of ASD. Overall, offspring of mother or father born with low birth weight or having gestational age < 37 completed weeks showed small elevated risks for ASD. The associations were slightly attenuated upon adjustment for factors that might affect the parental birth outcomes. Compared to the referent group, children born to mothers with low birth weight or were born prematurely had approximately 20% greater risk for ASD (low birth weight, OR=1.19, 95% CI: 1.03-1.38; preterm birth, OR=1.19, 95% CI= 1.01-1.40). Likewise, offspring of fathers with unfavorable birth outcomes had approximately 30% higher risk of developing ASD (low birth weight, OR=1.31, 95% CI= 1.07, 1.59; preterm birth, OR=1.29, 95% CI=1.06, 1.57). There were no consistent differences comparing these associations in the male and female offspring (Table 3). The effect estimates in girls were less precise due to a smaller number of female ASD cases.

Table 2. Associations of Parental Adverse Birth Outcomes and Risk of ASD in Offspring

Birth Outcomes	No.		Odds Ratios		
	ASD Cases	Noncases	Crude Associations (95% CI)	Adjusted (95% CI) [a]	Adjusted (95% CI) [b]
Mother (n=235,228)					
Low Birth Weight	205	12,544	1.25 (1.09, 1.45)	1.23 (1.07, 1.42)	1.19 (1.03, 1.38)
Preterm Birth	154	9,570	1.23 (1.04, 1.45)	1.23 (1.04, 1.44)	1.19 (1.01, 1.40)
Father (n=161,606)					
Low Birth Weight	108	6,976	1.35 (1.11, 1.64)	1.34 (1.10, 1.63)	1.31 (1.07, 1.59)
Preterm Birth	110	7,303	1.31 (1.08, 1.59)	1.32 (1.09, 1.60)	1.29 (1.06, 1.57)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth and place of residence at birth

[b] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery

Table 3. Adverse Parental Birth Outcomes and Risk of Offspring ASD, Stratified by Offspring Sex

Birth Outcomes	Male Offspring				Female Offspring			
	No		Odds Ratios		No		Odds Ratios	
	ASD Cases	Non-cases	Crude Associations (95% CI)	Adjusted[a] (95% CI)	ASD Cases	Non-cases	Crude Associations (95% CI)	Adjusted[a] (95% CI)
Mother (n=235,228)								
Low Birth Weight	166	6,309	1.29 (1.10, 1.52)	1.23 (1.05, 1.45)	39	6,227	1.15 (0.83, 1.59)	1.10 (0.79, 1.52)
Preterm Birth	120	4,867	1.20 (1.00, 1.45)	1.16 (0.96, 1.39)	34	4,696	1.34 (0.95, 1.89)	1.30 (0.92, 1.84)
Father (n=161,606)								
Low Birth Weight	83	3,591	1.27 (1.02, 1.59)	1.23 (0.99, 1.55)	25	3,385	1.64 (1.09, 2.47)	1.56 (1.04, 2.35)
Preterm Birth	91	3,732	1.35 (1.09, 1.67)	1.33 (1.08, 1.65)	19	3,571	1.16 (0.73, 1.84)	1.13 (0.71, 1.79)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery

The results remained unchanged when including only firstborn offspring (**Supplemental Table 1).** In analyses restricted to children with autistic disorder, a positive association for ASD risks in offspring was found for paternal preterm birth (OR=1.40, 95% CI: 1.01, 1.94) and paternal low birth weight (OR=1.44, 95% CI:1.04, 2.00), but the association was null for maternal adverse birth outcomes (**Supplemental Table 2)**. The effect estimates were similar assessing parental term low birth weight compared with normal weights (**Supplemental Table 3)**, while a higher risk estimate was found for mother (OR=2.17, 95%CI:1.43, 3.29) and father (OR=1.81, 95%CI:1.43, 3.29) who were born very preterm (<32 weeks) compared with parents born at full term (**Supplemental Table 4).** Results also remain largely unchanged while mutually adjusting for maternal or paternal birth outcomes, except for the association for maternal preterm birth and ASD risk in the offspring seem to be attenuated after controlling for paternal preterm birth status (**Supplemental Table 5)**.

4. Discussion

We conducted a prospective population-based cohort study to investigate intergenerational risk for ASD in association with parental preterm birth and low birth weight. The present analyses suggest that adverse birth outcomes of the fathers or the mothers might independently increase the risk of ASD in the next generation. Parents born very preterm, especially, marks a nearly 2-fold increase in ASD risk in their children. Results seem to indicate heterogeneity comparing autistic disorders to ASD, but a larger dataset is needed to disentangle the possible differences in ASD sub-phenotypes. Findings remained robust in other sensitivity analyses conducted.

Over the past years, there has been increasing interest in the consequences of prenatal exposures to environmental risks for subsequent generations. Previous studies reported heritable effects of exposures to a range of harmful environmental agents, including diethylstilbestrol,[17–20] tobacco,[21–23] and food supply.[24] One recent study reported an association between maternal intrauterine exposures to smoking and the risk of ASD in offspring.[28] However, to our knowledge, the present study is the first to explore the intergenerational effects of adverse birth outcomes of parents on ASD risk in children. Here, utilizing the DAG, we have also developed a possible causal framework for how parental adverse birth outcomes might be associated with ASD risks in the offspring. First, we proposed that adverse birth outcomes of parents might act as a proxy measure of extrinsic environmental conditions resulting in harmful exposures while *in utero*. The fact that the associations attenuated upon adjustment for grandmaternal sociodemographic and pregnancy-related factors supports our hypothesis that measured sociodemographic and pregnancy characteristics that can also affect parental harmful exposures *in utero* are partially responsible for the observed associations. Secondly, we identified an indirect path from birth outcomes of parents to offspring ASD, mediated via characteristics of parent's overall health and wellbeing in

adulthood. Parents born disadvantaged might also be more likely to have poorer physical health and lower socioeconomic achievement persisted into adulthood,[32–34] which in turn could influence disease risks in their children.

Evidence for germline mutations resulting from harmful intrauterine experiences has been accumulating in the literature. Prenatal exposures to harmful environmental agents and psychological stressors, including dichlorodiphenyltrichloroethane (DDT),[36] endocrine disrupting chemicals,[45] and stress[37,38] might lead to epigenetic modifications in the following generation. Narrowing the focus on offspring neurodevelopment, animal studies have provided support for this mechanism by demonstrating that early *in utero* exposures to nicotine alters gene expression and elicits behavioral and cognitive impairment in mouse models.[46,47] Therefore, it is probable that epigenetic changes as a result of adverse *in utero* exposures, which are marked by poor outcomes at birth, directly affect ASD risk in offspring.

The results of the study were based on a nationwide cohort comprising a large number of individuals in Denmark starting from 1978. All information on birth outcomes of parents were prospectively and independently collected when the mothers and fathers were registered at birth in the DMBR. This approach limits recall bias, and any measurement errors for paternal birth outcome status were expected to be random. Information on other sociodemographic characteristic were also obtained from routinely collected data by means of unique personal identifier,[40] which also limits recall bias. The diagnostic status of ASD was ascertained by trained psychiatrists based on ICD-10 diagnostic criteria,[48] and ASD diagnoses recorded in the Danish Psychiatric Central Register found to have high validity in a previous study.[43]

There are several caveats to the study. First, perinatal factors associated with intrauterine experiences, such as pre-pregnancy BMI and maternal smoking, were not collected until more

recent years in the Danish register thus were unavailable for anlayses.[40] The transgenerational risk estimates could be stronger if studies directly assess parental in-utero exposures that also has a strong impact on their germline mutations. Second, individuals with the most disadvantageous conditions who have not had children at the time of study were inevitably left out, leaving room for possible selection bias. Third, potential mediating effects from parental poorer birth outcomes via their overall health and well-being in adulthood were not examined in this study and should be evaluated in the future. Fourth, confounding and influence from heritable genetic factors should also be considered in the future framework.

Despite possible limitations, this study should be evaluated in light of its public health and clinical implications. Our findings enriched current understanding of the complex etiology of ASD, an impairing neurodevelopmental condition resulting in significant financial and psychological burdens worldwide. This study offered a new perspective on investigating multigenerational disease risks by identifying the potential of parental adverse outcomes at birth which are routinely collected in the medical health records as indicators for the effects of persistent sociodemographic disadvantages and harmful early life exposures. This proxy measure might provide the basis for future studies to measure extrinsic environmental conditions influencing the overall health of successive generations that are otherwise hard to quantify. Taken together, our findings underscored the importance of reducing social disparities to improve the future health of the next generation. In addition, our study provided insight into potential transgenerational epigenetic risks marked by adverse characteristics at birth. Future directions should involve collecting additional information on exposure and confounding factors related to *in utero* exposures of parents to examine if our hypothesized role of adverse parental birth outcomes and ASD risks in the offspring still holds true. Further mediation analyses should be performed to investigate whether the

mediating variables account for a significant amount of the total effects of parental adverse birth outcomes on offspring ASD; such analyses might help in differentiating between direct and indirect paths.

In conclusion, we find that children of parents with adverse birth outcomes are at small elevated risk of ASD diagnosis. The association is partially accounted for by measured grandmaternal sociodemographic and pregnancy-related characteristics, supporting our hypothesis that adverse parental birth outcomes might act as a proxy measurement of negative environmental influences on the developing brain and behavior that might be passed down to the following generation. Future studies should investigate both the genomic and non-genomic pathways leading to transgenerational risks of ASD.

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Supplementary material

Supplemental Table 1. Associations of Parental Adverse Birth Outcomes and Risk of ASD in Offspring, Firstborn Children Only

Birth Outcomes	No.		Odds Ratios	
	ASD Cases	Noncases	Crude Associations (95% CI)	Adjusted (95% CI)[a]
Mother				
Low Birth Weight	146	7,542	1.27 (1.07, 1.51)	1.22 (1.03, 1.45)
Preterm Birth	112	5,871	1.25 (1.03, 1.51)	1.22 (1.00, 1.48)
Father				
Low Birth Weight	72	4,377	1.24 (0.98, 1.58)	1.20 (0.95, 1.53)
Preterm Birth	77	4,541	1.28 (1.02, 1.62)	1.27 (1.00, 1.60)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery

Supplemental Table 2. Associations of Parental Adverse Birth Outcomes and Risk of ASD in Offspring, Children with Autistic Disorder Only

Birth Outcomes	No.		Odds Ratios	
	ASD Cases	Noncases	Crude Associations (95% CI)	Adjusted (95% CI)[a]
Mother				
Low Birth Weight	59	12,544	1.13 (0.87, 1.47)	1.03 (0.76, 1.40)
Preterm Birth	424	9,570	1.05 (0.77, 1.43)	1.05 (0.75, 1.49)
Father				
Low Birth Weight	39	6,976	1.49 (1.08, 2.07)	1.44 (1.04, 2.00)
Preterm Birth	39	7,303	1.42 (1.03, 1.97)	1.40 (1.01, 1.94)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery

Supplemental Table 3. Associations of Parental Term Low Birth Weight and Risk of ASD in Offspring

Birth Outcomes	No.		Odds Ratios	
	ASD Cases	Noncases	Crude Associations (95% CI)	Adjusted (95% CI)[a]
Mother				
Term Low Birth Weight	101	6,307	1.23 (1.01, 1.50)	1.17 (0.95, 1.43)
Father				
Term Low Birth Weight	40	2,797	1.25 (0.91, 1.72)	1.19 (0.87, 1.63)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery

Supplemental Table 4. Associations of Parental Very Preterm Birth and Risk of ASD in Offspring

Birth Outcomes	No.		Odds Ratios	
	ASD Cases	Noncases	Crude Associations (95% CI)	Adjusted (95% CI)[a]
Mother				
Very Preterm Birth	23	807	2.24 (1.48, 3.40)	2.17 (1.43, 3.29)
Father				
Very Preterm Birth	11	537	1.83 (1.01, 3.33)	1.81 (1.00, 3.30)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery

Supplemental Table 5. Associations of Parental Adverse Birth Outcomes and Risk of ASD in Offspring, Controlling for the Other Parent's Birth Outcome

Birth Outcomes	No.		Odds Ratios	
	ASD Cases	Noncases	Crude Associations (95% CI)	Adjusted (95% CI)[a]
Mother				
Low Birth Weight	92	6,462	1.20 (0.97, 1.49)	1.20 (0.97, 1.48)
Preterm Birth	64	5,001	1.08 (0.84, 1.39)	1.08 (0.84, 1.39)
Father				
Low Birth Weight	79	5,505	1.24 (0.99, 1.56)	1.24 (0.99, 1.56)
Preterm Birth	77	5,707	1.18 (0.94, 1.49)	1.18 (0.94, 1.49)

Abbreviations: ASD, Autism Spectrum Disorder

[a] Adjusted for year of birth, place of residence at birth, grandmaternal parity, grandmaternal education level, and grandmaternal age at delivery