A LASSO Analysis of Maternal, Obstetric, and Perinatal Predictors of Autism

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Abstract

Background. While genetics is clearly implicated in the etiology of autism, other biological factors may also increase the likelihood of an autism diagnosis. Many of these pertain to obstetric history and maternal medical conditions, but as they tend to co-occur it is difficult to ascertain which ones are most predictive of child's autism.

Methods. Women reported regarding their medical history and the pregnancy history of their first-born (N=557, 34.5% of children diagnosed with autism) and second-born (N=374, 28.1% of children diagnosed with autism) children. In Study 1, the first-born and second-born data were analyzed separately using LASSO, which enables the selection of variables most associated with child's autism. In Study 2, obstetric course and perinatal factors were compared for siblings discordant for autism (N mothers= 132, 61.7% males), thus allowing to control for many genetic and environmental aspects.

Results. Study 1 revealed maternal medical conditions, obstetric course factors, and perinatal factors predictive of child's autism (15 and 20 predictors for the first and second child analyses, respectively). Factors that replicated across the two pregnancies were among others, infertility, vaginal bleeding during pregnancy, and Type II diabetes. Study 2 revealed that maternal vaginal bleeding differentiated the pregnancy course of children later diagnosed with autism from neurotypical children.

Limitations. The medical information analyzed in this study is based on participants' recollection. While this approach allows to collect information regarding medical symptoms that may not have been logged in official medical records, participants might have forgotten relevant information. Future studies would benefit from combining self-report and health-provider recorded data.

Conclusions. This is one of few studies to analyze a large set of predictors, spanning maternal medical conditions, obstetric course, and perinatal factors. Analyzing these together, using machine-learning methods, allows us to disentangle the specific factors associated with child's autism. Study 2 enabled us to examine this within families, thus passively controlling for genetic and non-specific environmental effects. Our findings highlight the pregnancy course and maternal fertility factors which are of importance for predicting child's autism.

Introduction

Autism spectrum conditions are a set of neurodevelopmental conditions characterized by difficulties in social communication and interaction, and by restricted and repetitive interests and behaviors (1). The prevalence of autism in the United States is 1 in 54, with a male bias of 4:1(2). The etiology of the condition is thought to be a combination of genetic and non-genetic factors (3, 4). However, the specific factors, both genetic and environmental, are yet mostly unknown (5).

Previous research has shown that for environmental/non-genetic factors the timing of the exposure is critical, and most studies focus on early exposure – *in utero* or immediately after. Thus, prenatal and

obstetric factors, such as maternal medical conditions during pregnancy and obstetric complications (6); and early perinatal factors, such as pre-term labor and infant characteristics (7), seem to be strongly related to autism in the developing child. Even though many of these factors are interconnected or co-occurring, most of the available studies focus on a few selected predictors (e.g., (8–11)), which makes it harder to understand the unique association of each one (beyond the others) with autism. To address this problem, we focus on specific medical symptoms and conditions that have been previously associated with child's autism, and examine those within a single analysis using least absolute shrinkage and selection operator (12), which allows to choose variables most likely to be associated with the outcome from many potential predictors. We examined predictors of autism in the first and second-born children (Study 1) and compared siblings discordant for autism (Study 2). Our analyses focused on three groups of diagnoses; (1) Maternal medical factors include any diagnosis, typically chronic, the mother received in her lifetime. These may serve as proximal or distal factors in explaining child's autism. For example, Polycystic Ovary Syndrome (PCOS) is a maternal condition associated with child's autism(8, 13).This association has been interpreted as a consequence of maternal testosterone passing to the foetus and inducing neurological changes, which in turn, may trigger elevation of autistic traits and behavior (14, 15). (2) Obstetric factors include any diagnoses, conditions or symptoms that occur during and are related to pregnancy. For example, maternal infection during pregnancy (viral or bacterial) was previously associated with child's autism (16–18). Another such condition is infertility, which has been reported with mixed results (19–22). These mixed findings can be the result of an indirect association of fertility treatment and autism, mainly through an increase in the likelihood of obstetric complications, pre-term labor, and low birth-weight; through an association with maternal medical conditions such as PCOS (8); or through parental age (23). All these factors have been independently associated with child's autism(6, 7, 24). (3) Perinatal factors include characteristics of the child immediately after birth, such as gestational age. Gestational age was previously associated with autism (25), but also with various obstetric and maternal medical conditions (26).

The current study

As reviewed, many of the maternal medical conditions, obstetric conditions, and perinatal characteristics have been independently associated with autism, but are also interconnected or co-occurring (7, 25, 27–29). Only by examining a combination of predictors can we assess the relative contribution of each predictor above others and isolate the most relevant predictors. To this end, the current study utilizes information collected from a large group of women regarding their medical conditions and pregnancy course. We compare these factors for children later diagnosed with autism and children who are typically developing. Study 1 uses a data-driven, LASSO, approach to identify which conditions are associated with autism in the firstborn and second-born child, separately. Study 2 examines a sub-sample of mothers who reported on the obstetric course of births resulting in a typically developing child and a sibling later diagnosed with autism. We compare the siblings' obstetric course to isolate pregnancy-course related predictors of autism, while passively controlling for many non-specific environmental and genetic factors.

Methods

Participants- A total of N = 1,230 women aged 15–77 years (mean = 38.42, SD = 12.4) were recruited for a study on health through two websites managed by the Autism Research Centre (ARC) at Cambridge University, UK; 721 women through a website that targets individuals diagnosed with autism and their family members (https://autismresearchcentre.net/) and 509 women through a website targeting the general population (affiliation to ARC is not mentioned; https://cambridgepsychology.com). Of all the participants enrolled in the study, only mothers of biological children were included in the current analyses. Participants were provided with information regarding the study and gave their consent before gaining access to the questionnaire. The study was approved by the Psychology Research Ethical Committee (PREC) at Cambridge University. In current analyses only women who reported regarding at least one pregnancy resulting in a live birth were included (N = 572). Births of multiples and children whose diagnosis status was missing were excluded from analyses.

Study 1. Two separate analyses were conducted, for the first and second live-born child of each mother. The final sample included: (1) N = 557 mothers and their first-born children (four mothers were removed due to missing data regarding child's autism diagnosis; and 11 due to multiple fetuses). (2) N = 374 mothers and their second-born children (31 mothers were removed due to missing data regarding child's diagnosis; and 13 due to multiple fetuses).

Study 2. Analyses were conducted on a sub-sample of 132 mothers (264 pregnancies) who reported on at least one child diagnosed with autism and at least one typically developing child (TD). For each mother we selected the first reported single birth of a TD child and the first reported single birth of a child later diagnosed with autism. The siblings share a biological father, as determined by the maternal report regarding father's date of birth (see Table 1 for details).

Table 1
Sample composition-

	N mothers of a child diagnosed with autism	N mothers of a typically developing child	Total number of mothers	Parental mean age	N child male sex (% in sample)
First child	192 (34.5%)	365 (65.5%)	557	Mothers- 27.72 ± 5.7 Fathers- 30.61 ± 7	306 (54.9%)
Second child	105 (28.1%)	269 (71.9%)	374	Mothers- 30.28 ± 5.2 Fathers- 32.68 ± 6.1	213 (57%)
Sub-sample analysis	-	-	132	Mothers- 30.47 ± 5.3 Fathers- 32.71 ± 5.7	163 (61.7%)

Measures- Mothers filled out the following self-report measures:

(1) Demographic questionnaire - including mother's and father's date of birth, BMI before pregnancy, number of pregnancies, and autism diagnoses in the family.

(2) Health and pregnancy questionnaire (see Supplementary Information A) - maternal medical conditions (i.e. not specific to the pregnancy); conditions and complications during pregnancy; and infant characteristics. Only items relating to maternal medical conditions, obstetric course and perinatal factors were analyzed. See full list in Table 2 and Supplementary Information A.

Table 2
List of the independent variables used in each analysis

	First child	Second child	Sub sample analysis
Demographic information			
Mother autism diagnosis	X	X	
Family member autism diagnosis	X	X	
Mother's age at birth	X (0.4% imputed)	X	X
Father's age at birth	X (1.3% imputed)	X (0.5% imputed)	X
Percentage of pregnancies ended in miscarriage	X	X	
Maternal medical conditions			
Ovarian cancer	X	X	
Uterine cancer	X	X	
Breast cancer	X	X	
Chronic fatigue syndrome (CFS)	X	X	
Hyperthyroidism	X	X	
Hypothyroidism	X	X	
High cholesterol	X	X	
Autoimmune disorder	X	X	
Pre-menstrual syndrome (PMS)	X	X	
Polycystic ovary syndrome (PCOS)	X	X	
Cardiac conditions	X	X	
High blood pressure	X	X	
Anovulation (failure to ovulate)	X	X	
Type II diabetes	X	X	
Epilepsy	X		
Infertility	X	X	

	First child	Second child	Sub sample analysis
Sum of maternal medical conditions	X	X	
Obstetric course factors			
Infertility treatments	X	X	
Hormonal medications during pregnancy	X	X	
Infection	X	X	X
Maternal vaginal bleeding after second trimester	X	X	X
Blood sugar medications	X	X	
Maternal BMI prior to the pregnancy	X (21.5% imputed)	X (27% imputed)	X 20.5% imputed)
Maternal weight gain during pregnancy	X (36.4% imputed)	X (39.9% imputed)	X (34.5% imputed)
Gestational diabetes	X	X	
Preeclampsia	X	X	
Hyperemesis gravidarum	X	X	
Hypertension	X	X	
Polyhydramnios	X	X	
Placenta previa	X	X	
Placental abruption	X		
Infection amniotic sac	X		
Other conditions	X	X	
Sum maternal medical conditions during pregnancy	X	X	Pregnancy complication (yes/no)
Treatments for preterm labor	X	X	
Perinatal factors and infant's characteristics			
Child gestational age	X (8.6% imputed)	X (7.2% imputed)	X (5.3% imputed)

	First child	Second child	Sub sample analysis
Child sex	X	X	X

Notes: a) The prevalence of each condition in the sample was examined separately for each analysis. Each analysis included only variables with prevalence of more than 5 valid cases for binary variables and less than 40% missing value for quantitative variables. For each sample the variables included in the analysis are marked in X. b) In the sub sample, only obstetric factors and perinatal factors were included, as maternal characteristics are shared between children.

Data Analysis

Most of the predictor variables were treated as binary variables (yes/no), and few as ordinal or quantitative variables (see Supplementary Information A for more information).

Missing data imputation-Variables with less than 40% missing data (quantitative variables) or less than 5 cases (binary variables) were included in the analyses, and the missing data was imputed using “MICE” (Multivariate Imputation via Chained Equations) package in R, and the Predictive Mean Matching (PMM) technique, which is appropriate for numeric variables. MICE assumes missing at random, meaning that the probability that a value is missing depends only on other observed values, and therefore observed values can be used to predict the missing value. We used the MICE procedure to create 1,000 imputed data sets (30), and averaged out the imputed variables across the data sets.

Study 1

The main aim of the study was to examine the association between maternal medical conditions, obstetric factors and perinatal factors, with child's autism. To select the predictors which show a unique contribution to autism we analyzed the data using the procedure LASSO (in R, "glmnet" package; (31)).

LASSO (Least Absolute Shrinkage and Selection Operator) is a technique for regression analysis, which performs both variable selection and regularization; and can be used for binary outcomes (12). The technique uses L1 penalty, which minimizes the absolute value of each predictor by shrinking all estimates toward zero (31, 32). In the context of this research, the technique assigns positive and negative weights to variables associated with child's autism. Variables unrelated to the diagnosis are assigned a weight of zero, which effectively excludes them from the final model. LASSO yields a regularization parameter (a penalty; i.e "λ") that creates a parsimonious model which contains the maximum number of parameters and minimum cross-validation errors. The final model contains the selected predictive variables that were associated with the outcome. Despite some limitations (31, 33), LASSO has high accuracy, and the chosen variables are highly likely to represent true contributions (33), and therefore is a reliable method for predictors selection. Although the LASSO yields coefficient value for each predictive variables, one cannot interpret the relative magnitude of the coefficients, because LASSO

creates bias in the estimation of the parameters (due the shrinking toward zero), and the coefficients are not necessarily accurate. Therefore, an estimator was calculated for every coefficient by training LASSO classifiers on 1,000 bootstrapped samples of the data using the glmnet R package. To ensure a coefficient of zero for unrelated variables, the median of the coefficients for every variable, rather than the mean, was calculated as the final estimator. Additionally, a 95% confidence interval for the medians was calculated using scipy.stats.binom (34). To calculate the P value for every estimator, 10,000 equally-distributed random datasets were generated by independently bootstrapping each column of the original dataset. Then, a one-sided p-value was calculated for each estimator as the number of times the respective random coefficients were higher than or equal to the actual estimator (for positive estimators), or lower than or equal to the actual estimator for negative estimators, divided by the total number of random datasets (10,000). P values were not calculated for coefficients estimated to be 0.

Study 2

Ten predictors, which could differ between pregnancies, were included, negating the need for predictor selection. We conducted bootstrapped (5,000 repetition) paired t-test analysis to compare the rate of each condition for TD vs autistic siblings. A Bonferroni correction was applied to control for multiple testing (.05/10 = .005).

Results

Study 1:

A LASSO analysis was conducted for the first and second-born children separately. See descriptive statistics for each sample in Table 3. See summary of the predictors of child's autism in Table 4. For the first-born, the final model included 15 predictors associated with increased likelihood for autism diagnosis in the child For the second-born, the final model included 20 predictors of child's autism.

Table 3
Descriptive statistic by birth order group:

	Autism	TD
First child		
N	192	365
Male	145 (75.5%)	161 (44.1%)
Female	47 (24.5%)	204 (55.9%)
Mother's age at birth	28.72 ± 5.8	27.18 ± 5.6
Father's age at birth	31.83 ± 7.6	29.96 ± 6.6
Mother’s autism diagnosis	41 (21.4%)	72 (19.7%)
Second child		
N	105	269
Male	73 (69.5%)	140 (52%)
Female	32 (30.5%)	129 (48%)
Mother’s age at birth	30.75 ± 4.9	30.09 ± 5.4
Father’s age at birth	33.01 ± 5.6	32.56 ± 6.2
Mother’s autism diagnosis	21 (20.0%)	46 (17.1%)

Table 4

Results of the bootstrapped LASSO analysis, including the bootstrapped median coefficient and confidence intervals. Top panel – older child, bottom panel – younger child.

	Median coefficient	P value	95% C.I.	
			Lower	Upper
First child				
Maternal autism diagnosis	0	0.8360	-	-
Family member autism diagnosis	1.428	0.0010	1.401	1.448
Mother's age at birth	0.034	0.0620	0.032	0.036
Father's age at birth	0.020	0.1040	0.019	0.022
Percentage of pregnancies ended in miscarriage	-0.846	0.0130	-0.904	-0.783
Ovarian cancer	0	0.9830	-	-
Uterine cancer	0	0.9440	-	-
Breast cancer	0	0.9350	-	-
Chronic fatigue syndrome	0	0.9210	-	-
Hyperthyroidism	0	0.9880	-	-
Hypothyroidism	-1.147	0.0020	-1.192	-1.088
High cholesterol	0	0.9380	0	0.053
Autoimmune disorder	-0.228	0.0220	-0.286	-0.183
Pre-menstrual syndrome	0.113	0.0750	0.085	0.146
Polycystic ovary syndrome	0	0.8630	-	-
Cardiac conditions	0	0.9150	-	-
High blood pressure	0	0.9170	-	-
Anovulation	0.020	0.0160	0	0.085
Type ii diabetes	-2.684	0.0010	-2.828	-2.565
Epilepsy	0.958	0.0020	0.854	1.060
Infertility treatments	0	0.9090	-	-
Sum of maternal medical conditions	0.201	0.0270	0.186	0.216
Maternal bmi prior to the pregnancy	0.007	0.2380	0.005	0.010
Maternal weight gain during pregnancy	-0.002	0.3020	-0.004	-0.001

	Median coefficient	P value	95% C.I.	
			Lower	Upper
Infection	0.648	0.0030	0.618	0.677
Maternal vaginal bleeding after second trimester	0.066	0.0350	0.031	0.098
Blood sugar medications	0	0.9890	-	-
Hormonal medications during pregnancy	0.589	0.0030	0.528	0.648
Gestational diabetes	0	0.9450	-	-
Preeclampsia	0.042	0.0540	0	0.118
Hyperemesis gravidarum	0	0.9820	-	-
Hypertension	0	0.9320	-	-
Polyhydramnios	0	0.9650	-	-
Placenta previa	0	0.9560	-	-
Placental abruption	0	0.9670	-	-
Infection amniotic sac	0	0.9640	-	-
Other conditions	0.008	0.0660	0	0.052
Treatments for preterm labor	0	0.9510	-	-
Sum maternal medical conditions during pregnancy	0.303	0.0220	0.276	0.327
Child gestational age	-0.032	0.1390	-0.037	-0.028
Child sex	1.479	0.0010	1.456	1.502
Infertility (none)	-0.242	0.0280	-0.299	-0.185
Primary infertility	0	0.9000	-	-
Secondary infertility	0	0.8800	-	-
Second child				
Mother autism diagnosis	0.135	0.0650	0.102	0.181
Family member autism diagnosis	1.587	0.0010	1.554	1.614
Mother's age at birth	0.026	0.1460	0.023	0.029
Father's age at birth	0.009	0.2070	0.006	0.012
Percentage of pregnancies ended in miscarriage	-1.091	0.0250	-1.176	-0.955

	Median coefficient	P value	95% C.I.	
			Lower	Upper
Ovarian cancer	0	0.9930	-	-
Uterine cancer	-0.157	0.0180	-0.259	-0.086
Breast cancer	0.271	0.0140	0.200	0.361
Chronic fatigue syndrome	0.037	0.0230	0	0.132
Hyperthyroidism	0	0.9380	-	-
Hypothyroidism	0	0.8520	-	-
High cholesterol	0	0.9470	-	-
Autoimmune disorder	0	0.9480	-	-
Pre-menstrual syndrome	0	0.8970	-	-
Polycystic ovary syndrome	0	0.9420	-	-
Cardiac conditions	-1.369	0.0020	-1.450	-1.244
High blood pressure	0	0.8530	-	-
Anovulation	1.645	0.0000	1.563	1.768
Type ii diabetes	1.392	0.0010	1.198	1.511
Epilepsy	0	0.9690	-	-
Sum of maternal medical conditions	0.080	0.1000	0.060	0.094
Infertility treatments	1.587	0.0010	1.459	1.706
Maternal bmi prior to pregnancy	-0.002	0.2850	-0.007	0.001
Maternal weight gain during pregnancy	0.032	0.1080	0.030	0.035
Infection	0	0.8880	-	-
Maternal vaginal bleeding after second trimester	-0.819	0.0040	-0.884	-0.758
Blood sugar medications	0	0.9830	0	0.312
Hormonal medications during pregnancy	0.712	0.0040	0.627	0.790
Gestational diabetes	-0.834	0.0050	-0.965	-0.763
Preeclampsia	0	0.9530	-	-
Hyperemesis gravidarum	0	0.9830	-	-
Hypertension	-3.313	0.0000	-3.487	-3.010

	Median coefficient	P value	95% C.I.	
			Lower	Upper
Polyhydramnios	2.645	0.0000	2.535	2.783
Placenta previa	-0.230	0.0110	-0.339	-0.098
Other condition	0.586	0.0060	0.533	0.647
Sum of pregnancy conditions	0	0.7980	-	-
Treatments for preterm labor	-0.397	0.0070	-0.526	-0.281
Child's gestational age	0.064	0.0950	0.059	0.070
Child sex	1.029	0.0030	0.998	1.053
Infertility (none)	0.729	0.0060	0.575	0.843
Primary infertility	-1.003	0.0030	-1.136	-0.852
Secondary infertility	0	0.9590	-	-

Note: Significant findings are in bold.

Study 2:

132 parents and their 264 children were included in the analysis. See results in Table 5. In this analysis, only child-related variables were included (obstetric and perinatal factors), as maternal factors are shared by both children.

Table 5
Bootstrapped paired t-test analyses

				95% C.I.	
	Mean (SD)	**T**	**P value**	**Lower**	**Upper**
Birth order	.106 (.998)	1.221	.224	− .066	.278
Maternal age at birth	.341 (4.472)	.876	.383	− .429	1.111
Paternal age at birth	.318 (4.525)	.808	.421	− .461	1.097
Maternal pre-pregnancy BMI	.308 (3.725)	.949	.345	− .334	.949
Weight gain during pregnancy	.726 (12.405)	.672	.503	-1.410	2.862
Maternal vaginal bleeding after second trimester	.091 (.359)	2.907	.004	.029	.153
Infection during pregnancy	− .083 (.479)	-1.998	.048	− .166	− .001
Pregnancy complications	− .015 (.302)	− .576	.566	− .067	.037
Child’s gestational age	.091 (2.100)	.495	.621	− .271	.452
Child’s sex	− .295 (.662)	-5.125	.000	− .410	− .181

Discussion

Studies on maternal medical factors predicting child's autism tend to focus on few factors within the same analysis. This can be problematic as some of these factors are etiologically or phenomenologically dependent, which makes it harder to determine which factors can have the largest contribution to predicting child’s diagnosis. In Study 1, a case-control approach revealed 15 predictors of autism for the first-born, and eight of those were replicated in the second-born along with 12 additional predictors. In Study 2, we compared a subset of predictors, relating to pregnancy course and perinatal factors for siblings discordant for diagnosis. In this analysis two factors were significant, replicating those found in Study 1. Our analyses broadly showed that obstetric factors and maternal medical conditions were most predictive of child's autism. Below we will discuss the main findings.

Gestational bleeding during the second or third trimesters was associated with child’s autism in all analyses (yet the effect is small in the first-born), replicating previous studies (6). Gestational bleeding is a non-specific condition, and can indicate a host of other pregnancy complications, such as placental insufficiency and preeclampsia, which have also been associated with autism (26) (but were of low prevalence in the current study and should be studied further). Interestingly, a cumulative factor of pregnancy complications was significant only for the first, but not second-born, which may reflect an

indirect association through maternal age, as pregnancy complications are associated with older maternal age (29).

The current findings suggest that infertility, rather than infertility treatments and other obstetric conditions, is related to autism, as we find this effect after controlling for infertility treatments and multiple obstetric complications, some of which are independently related to autism. Previous findings regarding the association between autism and infertility and fertility treatments were mixed. One study (27) found a higher incidence of autism among children born after infertility treatments, as compared to natural conception. The association remained statistically significant even after adjusting for parity, infant gender, and parental age, all factors that are independently associated with both infertility treatments and autism. In contrast, Hvidtjørn and colleagues (2010) found no association between autism in children and infertility treatments, in a large cohort study. Other studies (22, 35) also didn't find any association between infertility treatments and autism diagnosis, in two separate studies conducted in California, USA. One hypothesis to explain the mixed findings is that infertility treatments are indirectly related to autism through an association with obstetric complications, pre-term labor, and low birth-weight, which are all factors that have been independently associated with an child's autism (6, 7, 24), and with older parental age (21, 36, 37). Parner and colleagues (2012) analyzed a cohort of all singleton births between 1980 to 2003 in Denmark and found that older parental age is associated with child's autism(38). Similarly, a cohort study of singleton births between 1989 to 2002 conducted in California, USA, also found that advanced parental age was associated with child's autism (39). Older maternal age may be associated with autism not only because of the increased risk of chromosomal abnormalities in the ova (6), but also due to the relationship between mature age and increased risk for pregnancy complications (29).

The current findings suggest that gestational diabetes and type II diabetes are both related to autism, but not BMI prior to pregnancy or weight gain during pregnancy. Previous studies found a relationship between various metabolic conditions such as maternal obesity prior to pregnancy, increased weight gain during pregnancy and gestational diabetes (defined as glucose intolerance with onset or first recognition during pregnancy) with autism and with general poor neurodevelopmental outcomes (40, 41). Krakowiak and colleagues found that mothers of children diagnosed with autism had a higher rate of gestational diabetes and obesity (defined as BMI > 30), compared to mothers of TD children (28). In addition, Xiang and colleagues found higher rates of child's autism among mothers diagnosed with type II diabetes before pregnancy, and among women diagnosed with gestational diabetes by 26 weeks of pregnancy (42). The current findings emphasize the importance of these metabolic conditions in autism.

The non-significant findings also shed light on the relative importance of various factors. Here we found no evidence for an association between child's gestational age and autism. Pre-term labor and low birth-weight were previously found to be non-specific risk-factors for neurodevelopmental and intellectual disabilities such as learning disabilities, attention problems, and poor executive function (25). According to one study, low birth-weight infants (< 2500 g) have a 60% increased likelihood of autism, and pre-term infants (< 32 weeks) had twice the chance of developing autism, for both sexes (31). In addition, Burstyn

and colleagues (2010) found that low birth-weight (< 2500 g) increased the likelihood for autism diagnosis by 33%. However, pre-term labor and low birth-weight often can be the consequents of obstetric complications (26), and the current findings emphasize the importance of obstetric complications over gestational age in predicting child's autism.

Immune system activation during pregnancy is another suspected environmental mechanism for child's autism. Animal studies show that immune activation during pregnancy is associated with abnormal brain development (16, 43). Specifically, Shi and colleagues found a reduction in social behavior and elevated anxiety behaviors among mice born to mothers infected by a virus during pregnancy (44). Studies in humans find similar associations. Lee and colleagues (2015) found that maternal infection (viral or bacterial) which leads to hospitalization, increased the likelihood for autism by 37%, in a cohort study of all live births born 1984–2007, in Sweden (17). However, another study found an association only for hospitalization due to bacterial infections(16, 45), and another found no association between infection and autism in a Danish population (46). We also do not find evidence for this effect in the current study. Only autoimmune disorders and only for the firstborn were related to child's autism, similar to other findings in the field (e.g., (9, 47, 48), but see (49, 50)).

Importantly, some maternal medical conditions which were found in previous research as associated with autism, were not found to be significant or did not replicate across the analyses. For example, maternal PCOS was found to be related to child's autism in multiple large-scale analyses (8, 13), but in our study was not significant.

Limitations

The main limitation of the study is the use of self-report, recollection data, as opposed to the use of medical records. It is possible that some conditions and diagnoses were misremembered or missed entirely. Therefore, the findings of the current study should be replicated using medical records in order to validate the findings. Another limitation of the study is the sample size, which did not allow to examine the relationship between child's autism and relatively rare disorders and conditions. A larger sample, or a sample biased to include reports of mothers who suffered specific serious health and obstetric complications would allow to focus on these effects.

Conclusions

Our findings emphasize the role of infertility, including miscarriages, and obstetric complications as predictive factors of autism, beyond typically correlated factors such parental age and vaginal bleeding. Thus, these findings are important in guiding further research into the involvement of infertility and obstetric complications in the etiology of autism.

Declarations

Ethics approval and consent to participate

The study was approved by the Psychology Research Ethical Committee (PREC) at Cambridge University

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available as at the time of data collection such permission was not sought from the participants, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MR designed the study, analyzed and interpreted the data, and wrote the paper. AP designed the study, collected the data, helped interpret the data and gave critical comments on the paper.

DA analyzed the data and wrote parts of the paper. TS helped interpret the data and provided critical comments on the paper. AR helped design the study and provided critical comments on the paper.

PS helped collect and curtate the data. ML and CA helped interpret the data and provided critical comments on the paper. AE helped with data analysis and provided critical comments on the paper.

SBC designed the study, interpreted the data, and provided critical comments on the paper. FU designed the study, helped with data analysis, interpreted the data, and wrote the paper.

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