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Stem-Skilled Parents and Autism Spectrum Disorder in Offspring: A Case-Control Study

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SUMMARY

Autism spectrum disorder (ASD) is a neurodevelopment disorder characterised by a range of deficits in two specific domains: social communication and social interaction and repetitive patterns of behaviour. Several studies have explored the link between ASD and STEM (science, technology, engineering and mathematics, or other mathematics-grounded disciplines), but results are still uncertain. Objective of the study was to estimate the potential role of systemising abilities in parents as a risk factor for ASD in the offspring, using the achievement of a degree in STEM disciplines as a proxy characteristic of the exposure. There were 1,316 participants overall. There were 658 incident consecutive cases of definite ASD, diagnosed in a Reference Centre for ASD in Italy, from 2001 to 2020. The main exposure variable was parental education level. The risk of ASD in the offspring associated with the main exposure variable and the exposure covariates (e.g. use of neurotropic drugs during the first trimester of the mother's pregnancy, perinatal outcomes of participants and/or preterm birth) was studied by using conditional logistic regression analysis. In addition, we carried out a mediation analysis to investigate whether and the extent to which covariates significantly associated with ASD risk mediate the relationship between parental education level and ASD in offspring. A STEM degree in parents was significantly associated with risk of ASD in offspring (OR 1.43, 95% CI 1.03-2.54). Familiarity was weakly associated with the risk of ASD (OR 1.33, 95% CI 1.00-1.66) and is the stronger mediator (PME 28%). Sensitivity analysis did not show deviations related to gender or ASD level.
Our study moves in the direction of confirming the risk of occurrence of ASD in the offspring of parents with elevated systemising abilities.

Keywords: Autism spectrum disorder (ASD); STEM disciplines; systemising abilities; ASD risk in offspring.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The literature supports association between ASD and STEM disciplines (science, technology, engineering and mathematics, or other mathematics-grounded disciplines): this study gives a sound contribution to the debate and, overall, contributes to enrich knowledge and eventually leads to advances in information on the aetiology of ASD.
- The design and the sample size of the study allow well-powered conclusions, although larger samples are required to investigate more possible confounders and effect modifiers
- The main limitation is the lack of variables such as environmental or dietary exposures or genetic profiling. In addition, a prospective study following STEM graduates over time and monitoring offspring would be optimal, although inefficient.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopment disorder that emerges in early childhood, characterised by a range of deficits in two specific domains: social communication and social

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interaction and repetitive patterns of behaviour [1]. ASD is considered a medical condition that gives rise to disability as well as an example of human neurological variation ('neurodiversity') that defines a person's identity, with cognitive assets and challenges [2-3].

The epidemiological interest in ASD has increased because of its growing awareness in Western countries, documented in terms of both clinical research and public health attention [4]. Epidemiological research has highlighted the impact of ASD all over the world [5]. Regarding the United States, the surveillance system network of 11 states [6] estimated an overall prevalence of ASD of 1.68% (2.66% males and 0.66% females, with a male to female ratio of 4:1). The average prevalence of ASD in the European Union program is reported as 1.0% [7]. Indeed, in the last decades ASD diagnoses have at least doubled: in addition to a true increase in prevalence, the literature proposes alternative explanations, including changing diagnostic criteria, different methods of ascertainment, inhomogeneous protocols of diagnosis, research protocols, environmental components, cultural factors or awareness in recent years [8]. In any case, research is attempting to understand the aetiology of ASD, in terms of the epigenetic, neurobiological, genetic, neurological and hormonal factors at the base of this complex condition. There is no agreement about the causes of autism, and the aetiopathogenetic factors of ASD remain unknown. According to Stubbs and collaborators [9] and to Lai et al. [2] , the interactions between genetic and environmental factors are thought to contribute to its causes. There have been numerous studies showing that there is increased risk of neuropsychiatric disorders in offspring due to prenatal and perinatal environmental exposures [10]: nonetheless, genetic factors likely have an important role in ASD development. Specific thinking style [11] and impaired ability in reading intentions of others (theory of mind), which can be considered pathognomonic of ASD, as well as uncommon calculation abilities in a variable proportion of people with ASD, are characteristics strongly correlated with the brain attitude in systemising. This suggests that some of the genes for autism may be regulators of the systemising abilities of the brain, which can be expressed as a continuum regarding the ability to systemise. Moreover, genes can be expressed in first degree relatives that lead to a talent in systemising, thus individuating a trans-generational 'broader phenotype'.

A good proxy descriptor for systemising abilities is the attitude of parents to the so-called STEM disciplines (science, technology, engineering and mathematics, or other mathematics-grounded disciplines). This view has moved ASD research into an understudied area of interest: is ASD more common in the offspring of parents who show high-level skills in systemising abilities and who reach high education levels in the STEM disciplines? In most analytical studies [12] researchers have focused primarily on rates of autism among offspring of adults in the STEM domain; they suggest an elevated prevalence of autisti99c probands and relatives in STEM-related careers [13-15]. In a similar vein, a population-based study of the tech-heavy San Francisco Bay Area suggests that maternal STEM careers are associated with a higher prevalence of offspring with autism, though the researchers found no paternal STEM career choice or joint effects [16].

Some descriptive studies have explored the issue of ASD and STEM, focusing on the hypothesis that autism rates are higher in regions that have a high concentration of jobs in the STEM domain. Roelfsema et al. [17] reported that the prevalence estimates of ASD in an information technology (IT) area in the Netherlands was at least two- to fourfold higher than in non-IT areas, while the prevalence for the control conditions were similar in all regions. The authors underlined that these results are in line with the idea that in regions where parents gravitate towards jobs that involve strong 'systemising', such as the IT sector, there will be a higher rate of autism among their children. However, it is worth noting that conclusions from descriptive epidemiological studies whose objective is to compare prevalence rates of ASD across different areas are possibly jeopardised by relevant biases, like over- or under-diagnosis of borderline cases due to broader clinical criteria, or different awareness about autism in a cross-cultural perspective.

The literature suggests that many professionals in highly systemised occupations who excel in their fields have undiagnosed high-functioning ASD [18-19]. Baron-Cohen et al. [20] demonstrated that a group of undergraduate students with majors in science and mathematics scored significantly higher on all areas of the Autism Quotient (AQ) scale compared with classmates with other majors. Given the 'broader phenotype' symptoms of ASD seen in some parents of children with ASD, some researchers have proposed that these parents have highly technical and structured occupations in fields such as science, engineering and accounting [21-23]. For example, Jarrold and Routh [12] analysed data from Baron-Cohen et al. [21] and reported that occupations in engineering, accounting, science and medicine were more frequent in fathers of children with ASD. Notably, Windham et al. [16] demonstrated in a population-based study in California that the risk of having a child with ASD was almost twofold greater for mothers in highly technical occupations.

Dickerson et al. [24] found that fathers in health care and finance were more likely to have children with ASD; moreover, joint effects of parental technical occupations were associated with communication and social impairment: the results from this study support that a 'broader phenotype' and a sort of 'assortative mating' in adults with autism-like characteristics might contribute to intergenerational transmission of ASD, thus providing, at least, a minimal basis for new genetic models of autism. Overall, the issue of the association between STEM and ASD remains uncertain, and the literature recommends further studies on this topic.

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OBJECTIVE

Objective of the study was to estimate the potential role of optimizing abilities in parents as a risk factor for ASD in the offspring, using the achievement of a degree in STEM disciplines as a proxy characteristic of the exposure.

METHODS

Design and Conduct

We designed and conducted a retrospective case-control study based on population data from registry and outpatient records. The retrospective design was dictated by the relatively low incidence of ASD among the general population. This case-control study was based on incident cases recruited in a specialised centre in Italy and included in an epidemiological registry from 2001 to 2020. The conduct of the study includes the period 2014-2020.

Study Population

There were 1,316 participants overall. There were 658 incident consecutive cases of definite ASD, diagnosed at the Regional Reference Centre for ASD in L'Aquila, Italy, from 2001 to 2020. Diagnosis was made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders IV* [25]– or the *DSM-5* [1] after 2013 – and the cut-off values of the Autism Diagnostic Observation Schedule (ADOS) score, first edition [26] or second edition [27] after 2012. In 352 out of 658 cases (53.5%), the individuals were residents in the administrative area of L'Aquila and 0–18 years old, according to the epidemiological registry of the centre [28]. In 306 out of 658 cases (46.5%), the individuals were in the age range of 3–29 years, not resident in the same area and recruited from the autism outpatient clinic of the centre. Given the specific objective of the study and the design, there was no need to define exclusion criteria. There were 475 male cases (mean age at diagnosis 4.2 years, *SD* 2.1 years, range 2–28 years) and 183 female cases (mean age at diagnosis 4.7 years, *SD* 2.7 years, range 2–29 years). With regard to severity, the DSM-5 classifies cases in three levels (level 1, "requiring support"; level 2, "requiring substantial support"; level 3, "requiring very substantial support"): using the *DSM-5* criteria directly (for cases recruited or followed up after 2013) or by indirect attribution (for cases recruited before 2013), 127 out of 658 cases (19.3%), 98 males and 29 females, were classified as level 1; 304 (46.2%), 230 males and 74 females, were classified as level 2; and 227 (34.5%), 147 males and 80 females, were classified as level 3.

Controls were consecutive subjects who had first access to the same centre for clinical observation and diagnosis during the period of 2014–2020, but who did not meet fulfil the criteria for a formal diagnosis of ASD. Thus, 658 sex- and age-matched (± 1 year) controls (males: n = 475, M_{age} = 4.4, SD_{age} = 2.0, range 3–28 years; females: n = 183, M_{age} = 4.4, SD_{age} = 2.4, range 2–29 years) were recruited. No control subjects received an ASD diagnosis during the conduct of the study; 351 controls remained without any other diagnosis, and 307 received diagnoses including intellectual disability, language disorder, attention-deficit/hyperactivity disorder, specific learning disorder, unspecified neurodevelopmental disorder or schizophrenia spectrum disorders.

Patient and Public Involvement

Participants were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Exposure

Data were obtained both by clinical records and personal interviews of parents or legal tutors and collected through a closed-answer questionnaire. Considering that cases had been diagnosed and recruited in the register since 2001, information for cases diagnosed before 2014 was obtained by parental interview at the first follow-up observation during the conduct of the study (i.e. in the time lapse of 2014–2020). Interviews were conducted by a team of operators trained in data collection. The same questionnaire was also given to the parents of control subjects by the same team of operators at the time of the first access to clinical examination. The main exposure variable was parental education level (primary or lower secondary, upper secondary, degree/master in STEM or other discipline).

Mediator variables

We obtained information on several variables considered to be established risk factors related to ASD and evaluated these factors as potential mediators. The questionnaire included the following key covariates: use of neurotropic drugs during the first trimester of the mother's pregnancy (i.e. continuous use by specific medical prescription: yes or no); perinatal outcomes of participants (low birthweight [< 2,500 g] and/or preterm birth [< 37 weeks of gestation]: yes or no), housing and parents' work as a proxy indicator of socioeconomic status (low, middle and elevated); and familiarity, including both ascendants and collaterals, for ASD or other neurodevelopmental or psychiatric disorder (yes or no).

Ethics Approval

All parents or legal tutors of both cases and

controls agreed to participate in the study. The study was approved by the Ethical Committee of the Local Health Agency (Comitato Etico Province di L'Aquila e Teramo, Approval number: reference protocol 52505/21, approval decree no. 1348/21). The study was conducted according to the principles of the Declaration of Helsinki.

Statistical Analysis

The risk of ASD in the offspring associated with the main exposure variable and the exposure covariates was studied by conditional logistic regression analysis. Adjustment for odds ratio (OR) estimates included all covariates determined to be a potential confounder by having a *p* value < .20 and changing the point estimate for technical classification by at least 10%. Missing covariates were accounted for by multiple imputation. The 95% confidence intervals (CI) for ORs were calculated by using Woolf's method. The effects of the polychotomous predictive variables were modelled by creating a set of dummy indicators [29-30].

We also carried out a sensitivity analysis, stratifying by offspring sex, to evaluate potential sex-specific associations. Moreover, we performed analyses restricted to level 1 (high-functioning) ASD cases – that is, the clinical subtype frequently exhibiting systemising abilities – to address heterogeneity of ASD.

Finally, we carried out a mediation analysis to investigate whether and the extent to which covariates found to be significantly associated with ASD risk mediate the relationship between parental education level and ASD in offspring. A regression-based approach under the counterfactual framework was used to perform the analysis, and the total effect of the exposure was decomposed to a controlled direct effect and an indirect effect. The controlled direct effect indicated the change in offspring ASD risk when the mediator was controlled at the reference level (e.g. without the presence of the mediator) and the exposure was changed from the reference to the index level. The indirect effect indicated the effect of the exposure that acted through the pre-specified mediator when the exposure was fixed to the reference. The proportion mediated estimate (PME), the measure of the proportion of the total effect of the exposure mediated by the intermediate variable on the log odds scale, was also calculated. If the PME is small, then the question is what are the other pathways through which the exposure affects the outcome, other than being a mediator. By contrast, if the PME is large, the total effect of the exposure on the outcome is through the mediator.

RESULTS

Risk of ASD in Offspring

Matching by age and sex ensured similar demographic characteristics of cases and controls. Table 1 describes the main characteristics of exposures for both groups and the results of logistic regression analysis.

Table 1. Conditional logistic regression: risk estimates (OR) of ASD for all exposures

Exposure variables	Exposure level	Cases	Controls	Unadjusted OR (95% confidence interval)	Adjusted OR (95% confidence interval)
Educational level of parents (highest between father or mother)	Low/middle	124	138	1.0*	1.0*
	Licence	345	381	1.01 (0.76-1.34)	0.95 (0.80-1.21)
	Degree (other)	73	79	1.03 (0.69-1.53)	0.94 (0.67-1.44)
	Degree (STEM)	116	60	**2.15 (1.45-3.19)**	**1.48 (1.03-2.55)**
	total	658	658		
Use of neurotropic drugs during mother's pregnancy	No	337	380	1.0*	1.0*
	Yes	39	52	0.85 (0.54-1.31)	0.90 (0.59-1.26)
	total	376°	432°		
Perinatal outcome (low birthweight and/or preterm birth)	No	321	357	1.0*	1.0*
	Yes	111	86	**1.43 (1.04-1.97)**	**1.29 (1.00-1.66)**
	total	432°	443°		
Socioeconomic status	Low	260	241	1.0*	1.0*
	Middle	281	291	0.90 (0.70-1.14)	0.92 (0.75-1.09)
	High	116	125	0.86 (0.63-1.17)	0.91 (0.68-1.06)
	total	658	658		
Familiarity	No	565	592	1.0*	1.0*
	Yes	92	66	**1.46 (1.04-2.04)**	**1.33 (1.00-1.88)**
	total	658	658		

*reference category
°totals are lower than the overall number of participants due to missing information

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Regarding the education level of parents, 189 out of 658 (28.7%) cases have at least one parent with a degree, compared with 139 out of 658 (21.1%) controls: this difference increases when considering only the STEM disciplines (116 out of 658 cases, 17.6%, vs 60 out of 658 controls, 9.1%), which comprise the majority of all degrees in parents of cases (116 out of 189, 61.4%) compared with the parents of controls (60 out of 139, 43.1%). After adjusting for all covariates, a parent with a STEM degree was significantly associated with risk of ASD in offspring, although the strength of association is low, as shown by interval estimates of the OR (1.43, 95% CI [1.03, 2.54]). Familiarity was associated significantly with the risk of ASD, although at the limit level (OR 1.33, 95% CI [1.00, 2.18]). Perinatal outcome (low birthweight and/or preterm birth) was associated significantly with risk of ASD at the limit level (OR 1.29, 95% CI [1.00, 1.66]). None of the other covariates were determinants of ASD risk in offspring.

Sensitivity Analysis

We did not find deviations from the overall analysis comparing the risk association in males and females, or when considering only level 1 ASD cases.

Mediation Analysis

Table 2 shows controlled direct and indirect effect ORs and PME. Familiarity was the strongest mediator on ASD risk in offspring (PME 28.0%). A weaker mediation effect was observed for perinatal outcomes (PME 11.5%).

Table 2 - Estimated direct and indirect effects of mediators on the association between main exposure and risk of autism spectrum disorder (ASD) in offspring. Only covariates significantly associated with ASD risk were considered in the model.

Main Exposure	Mediators	Controlled direct effect [a] OR (95% CI)	Indirect effect [b] OR (95% CI)	Proportion mediated estimate (PME)
Parent education Level (STEM)				
	Perinatal outcomes (low birthweight and/ or preterm birth)	1.35 (1.02-1.70)	1.06 (1.00-1.14)	11.5%
	Familiarity	1.51 (1.10-1.96)	1.10 (1.05-1.18)	28.0%

a. The controlled direct effect indicates the change in offspring ASD risk when the mediator was controlled at the reference level (e.g. without the presence of the mediating factor) and the exposure was changed from the reference to the index level.

b. The natural indirect effect indicates the effect of the exposure that acts through the mediator when the exposure was fixed to the reference.

DISCUSSION

We have addressed a topic of increasing interest in recent years – the risk of ASD in the offspring of parents with elevated systemising abilities – by using the achievement of a degree in STEM disciplines as a proxy characteristic. The idea that individuals with ASD might be predisposed to choosing and succeeding in STEM-related majors and jobs has gained a footing in the scientific literature [31-32]. We found that having a parent a STEM degree was significantly associated with ASD in offspring: 61.4% (116/189) of parents of individuals with ASD with a degree had chosen STEM disciplines. In addition, familiarity was associated significantly with ASD, as confirmed by the mediation analysis between parental education level and children with ASD. In this analysis, familiarity was the strongest mediator on ASD risk in offspring.

We also found that perinatal outcome (low birthweight and/or preterm birth) was associated significantly with ASD at the limit level. In the mediation analysis, however, this variable had a weaker mediation effect. These findings are in line with the literature, although the topic is still complex. Indeed, research has for some time now supported the link between autism and scientific disciplines [33]. Baron-Cohen et al. [34] reported the first-ever prospective study of a child born from adults with a formal diagnosis of Asperger syndrome (the child's parents were both scientists).

In the wake of these results, Dickerson et al. [24] showed that fathers of children with ASD were more than twice as likely to be engineers compared with fathers of children typical development. Furthermore, in a population-based study in San Francisco, Windham and collaborators [16] demonstrated that the risk of having a child with ASD was almost two times greater for mothers in highly technical occupations. However,

past research about parental occupation and ASD have yielded conflicting results. Specifically, Jarrold and collaborators [14] argued that previous research had not account for other systemising occupations in their analysis, showing that fathers of children in the same sample were also more likely to be accountants, scientists and physicians. Dickerson and collaborators [24] showed that after adjusting for demographic variables in their analysis, the higher likelihood of having children with ASD for parents who are engineers was no longer statistically significant. However, this increased likelihood of having a child with ASD remained significant for fathers employed in the fields of health care and accounting/financial analysis, even when accounting for demographic variables. Thus, to prevent possible biases due to socioeconomic abilities in seeking diagnosis and obtaining treatment for children with ASD, Dickenson et al. [24] also assessed the relationship between workers in an office or professional environment versus workers in manual jobs, as well as ≥ 16 years of education and having a child with ASD. They found no associations. They also found no significant relationship between paternal, maternal or joint technical occupation characteristics and ASD diagnosis. Windham et al. [16] also considered the socioeconomic status of parents; they found no significant association with paternal technical occupation and ASD diagnosis of offspring. On the contrary, they found a significant association between maternal occupations in highly technical fields and having offspring with ASD, with sustained significance in mothers in computer programming.

This research topic is still widely debated, but the unanimous result in the literature is that individuals with ASD are more likely than the general population and other groups of disabilities to gravitate towards STEM. Our manuscript goes in the direction of confirming the risk of occurrence of ASD in the offspring of parents with elevated systemising abilities. Van der Zee and Derksen [35] emphasised the power of systematisation in autism. The authors support that high systemising abilities are characteristic in autism. Systemising expands folk physics by understanding the laws or rules governing non-causal systems. Systematic thinking is correlated strongly with interests and predisposition to scientific studies. Systemising refers to involving or using a system. A system is anything that takes inputs and delivers outputs that the human brain can analyse, for example, technical systems (computer), abstract systems (mathematics), social systems (business) or organisable systems (library) [36-37]. Systemising allows the brain to predict that event x will occur with probability *p* [22]. Systemising is considered the most powerful way to predict change, because it involves the search for patterns. Several studies suggest that individuals with ASD have their systemising mechanism set at levels above those in the typical population. When one's systemising level is above average, this person could be considered to be immersed in the world of things rather than people. The reason for a higher systemising level in autism could be due to the idea that systemising increases the feeling of control [38]. In fact, we know that for people with autism it is more reassuring to control events and to avoid forms of the unexpected. Despite the published results and the scientific interest about this topic, we need further confirmation and other studies.

There are several limitations of our study.

First, the main limitation is the lack of important variables such as environmental or dietary exposures or genetic profiling. Although it is true that several studies have proposed a co-partnership between genetic and environmental factors as the aetiology of autism, these have never been specifically determined, but only highly suspected by indirect means. However, no responsible gene has ever been identified to date. None of genetic or 'growth ' hypotheses are taken into account as variables for this study.

Second, a highly schematic discipline may be a likely career choice for a person with ASD, precisely because of the forma mentis underlying the autistic spectrum: a predilection for repetitive patterns, difficulty in social interactions and difficulty in the act of "reading between the lines" (the individual with autism tends to stop at the primary and immediate meaning of sentences, without a more "metaphorical" reading). The individual would therefore do well to work in a STEM discipline, because it is systematic and easier to understand effectively. This implies that a not negligible proportion of parents is likely to have a profile overlapping the autistic spectrum and this may represent a source of relevant bias.

Third, the main exposure variable taken into account in the study is the cultural level of the parents, divided into low/medium, diploma, degree, STEM degree. This variable is heterogeneous between both parents and can lead to significant bias, i.e. the possibility of under- or over-diagnosis of the spectrum: the sensitivity to the topic by parents from different cultural backgrounds is not equal, even for simple knowledge of the existence of the disorder, especially if it is not severe.

Finally, there are inherent difficulties in the definition of ASD [39].

Last, we believe that a prospective study following STEM graduates over time and monitoring offspring would be optimal - although inefficient and expensive – if compared with a case-control study.

Future research should record the parental occupation at the time of the child's birth and at the time of clinical assessment in larger samples to investigate more possible confounders and effect modifiers. Moreover, more data about the professional training of parents (e.g. college majors and degrees earned) should be collected to further assess their inclination to choose highly structured career paths regardless of whether they eventually enter the workforce. These studies should contribute to enrich knowledge and eventually lead to advances in information on the aetiology of ASD.

Paper invited by Dr. Carlo La Vecchia, Editor-in-chief EBPH

CONTRIBUTORSHIP

Valenti M and Mazza M conceived, supervised and reviewed the study, finalized the manuscript and edited the paper. Attanasio M, Le Donne I and Bologna A collected and interpreted the data and gave substantial contribution in writing the paper; Masedu F and Tiberti S analysed the data, reviewed, critically revised and finalized the paper.

COMPETING INTERESTS

Authors have not competing interests.

FUNDING

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DATA SHARING

Data will be available upon reasonable request.

ETHICS APPROVAL

The study was approved by the Ethical Committee of the Local Health Agency (Comitato Etico Province di L'Aquila e Teramo, Approval number: reference protocol 52505/21, approval decree no. 1348/21).

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