Original Article

Association between Prenatal Environmental Factors and Child Autism: A Case Control Study in Tianjin, China*

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Abstract

Objective To investigate the association between autism and prenatal environmental risk factors.

Methods A case-control study was conducted among 193 children with autism from the special educational schools and 733 typical development controls matched by age and gender by using questionnaire in Tianjin from 2007 to 2012. Statistical analysis included quick unbiased efficient statistical tree (QUEST) and logistic regression in SPSS 20.0.

Results There were four predictors by QUEST and the logistic regression analysis, maternal air conditioner use during pregnancy (OR=0.316, 95% CI: 0.215-0.463) was the single first-level node (χ^2=50.994, *P*=0.000); newborn complications (OR=4.277, 95% CI: 2.314-7.908) and paternal consumption of freshwater fish (OR=0.383, 95% CI: 0.256-0.573) were second-layer predictors (χ^2=45.248, *P*=0.000; χ^2=24.212, *P*=0.000); and maternal depression (OR=4.822, 95% CI: 3.047-7.631) was the single third-level predictor (χ^2=23.835, *P*=0.000). The prediction accuracy of the tree was 89.2%.

Conclusion The air conditioner use during pregnancy and paternal freshwater fish diet might be beneficial for the prevention of autism, while newborn complications and maternal depression might be the risk factors.

Key words: Autism; Environmental risk factors; Case-control study; Child health

Biomed Environ Sci, 2015; 28(9): 642-650 *doi: 10.3967/bes2015.090* *ISSN: 0895-3988*

www.besjournal.com (full text) *CN: 11-2816/Q*

INTRODUCTION

Autism is a type of intractable and persisting developmental disorder of neurological system[1], which includes a group of neurodevelopmental disorders characterized by varying degrees of impaired socialization, reduced communication, and limited, repetitive, or stereotyped interests and activities[2]. The current prevalence of autism is 14.7 out of 1000 eight-year-old children according to the report of Autism and Developmental Disabilities Monitoring (ADDM) Network in USA in 2010[3], and the prevalence was four times higher in males than in females[4]. Our understanding of the genesis and characteristics of autism was improved significantly in the past decade[5]. A strong genetic contribution has been recognized based on recurrence rates in siblings of autistic children and the greater concordance of monozygotic compared with dizygotic twins[6-7]. The comorbidity rate of autism is 60%-92% in monozygotic twins, compared with only

*The study was support by the National Natural Science Foundation of China Grant No. 81072313.

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0-10% in dizygotic twins, indicating the important role of genetic factors in the pathogenesis of autism[8]. However, twin concordance research recently suggested that environmental causes are also important[9] and are likely to contribute to the risk and severity of this condition[10]. The present understanding is that autism is likely to be a polygenetic disease with environmental factors interacting with genetic factors[11-12].

It is now widely accepted that the macroscopic and microscopic pathology or dysfunctions of brain underlies autism pathogenesis[13]. A variety of dysfunctions of brain may be related to the abnormality of fetus or infancy[14], due to pre-conceptual, prenatal or neonatal exposures[15], such as cadmium, nickel, trichloroethylene[15-16]. No single environmental factor has been identified to account for all autism cases[16], although a handful of environmental risk factors have been suggested based on data from human studies and animal research[17-18], including metabolic conditions (diabetes, hypertension, and obesity) during pregnancy[17], and the roles played by environmental risk factors are yet to be identified[16].

Because of the complex nature of autism pathogenesis, machine-learning algorithms are expected to be useful to model and predict its occurrence, such as decision trees, which are formed through recursive partitioning and dividing the data based on the values of a selected attribute[19]. The decision tree model searches for and finds the main factors influencing a dependent variable[20]. A two-fork tree algorithm, namely Quick, Unbiased, Efficient Statistical Tree (QUEST) developed by Loh and Shih[21] is more fast and less prone to has biases than other exhaustive search methods, such as classification and regression trees[22]. In the QUEST algorithm, variable selection and bifurcation point selection remain separated, and can be applied to any type of independent variables with negligible bias on selection of variables[23]. As to hierarchical data, decision tree is not considered as the hierarchical structure of the data, therefore it is more comprehensive and suitable for us to combine QUEST with other methods. Logistic regression analysis has also been widely used to find association between the outcome and the most important exposure variable in epidemiological studies, which is an ideal supplement[24].

The aim of this study was: 1) to identify the main environmental (non-genetic) risk factors on the basis of summarizing the previous related studies by the self administrated questionnaire, using the combination of QUEST and logistic regression analysis; and 2) to investigate the interactions between those variables.

METHODS

Study Subjects

A case-control study was conducted in Tianjin, China. The autism cases were selected from the special educational schools in Tianjin from 2007 to 2012. There were 11 special educational schools affiliated to China Disabled Persons' Federation (CDPF) in Tianjin, including 6 schools in downtown and 5 schools in suburb.

A total of 193 autistic children were enrolled in this study, among whom 122 were selected from 687 school-aged children (aged ≥7 years) from 7 schools; and 71 were pre-school aged children (aged <7 years), selected from four rehabilitation facilities for autistic children in Tianjin.

A questionnaire survey was conducted among the parents of autistic children to collect the information about the environmental risk factors from 12-months before mothers' pregnancy to the time when their children were diagnosed with autism. The questionnaire included potential risk factors based both on systematic analysis on previous studies[8,25-26] and our early work[27]. The case group included the children diagnosed by pediatrician according to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-4) and those with childhood autism rating scale (CARS) score ≥30. The control group included 733 typical development (TD) children and adolescents matched to cases by age and sex selected from the public kindergartens, elementary schools, junior high schools or high schools in the same areas in Tianjin. The inclusion criteria for controls included normal intelligence, normal development, and no physical and mental illness with the confirmation from the class teacher or school doctor.

Questionnaire

The research staff first explained the purpose and significance of the study to the teachers and parents, and then handed out consent forms to every parent of the study to inform them study procedures and the policies of confidentiality agreement. Self-reported questionnaire was used for all the cases and controls whose parents had signed

the consent forms. The parents of both groups were required to fill in the questionnaire with the guidance of trained research staff. The research staff explained the questionnaire to the parents and answered their every questions to minimize confusion and misunderstanding. All the questionnaires were collected at the investigation sites (in special educational schools for cases or normal schools for controls). The quality of the questionnaire data was then evaluated, and the returned questionnaires with two more answers for question or more than 10% of unanswered questions, or with same or wave shaped like answer selections were considered invalid.

Risk Factors

The following potential risk factors for autism were investigated in this study:

Parental Characteristics Parental characteristics included factors such as parental ages at delivery, ethnicity (Han or other minority groups), occupation, education background (college or above), marriage between close relatives, gravidity, exposure to toxins, cosmetic use, living environment, personality (introverted, extroverted or neutral), personal medical history and family history of dementia, retardation, mental illness, epilepsy, chromosomal disorders, and diabetes. Among those factors, living environment refers to both outdoor environment (whether there were factory, garbage station, industrial pollutant or high voltage transformer) and indoor environment (whether air conditioner, microwave oven or electromagnetic furnace were used; how long and how often were they used).

Binary variables were assigned to indicate whether parental age is advanced, the value 1 indicated that the parents were aged >30 years, and value 0 indicated that the parents were aged <30 years, according to our previous study[27]. For some questions, the subjects were asked to provide more details, for example, the type and brand of cosmetic and use frequency.

Prenatal Risk Factors Maternal characteristics and behaviors during pregnancy were considered in this study, such as smoking and passive smoking exposure, alcohol consumption, exposure to X-rays, computer use, use of tocolysis therapy, attempt to terminate pregnancy, contact with toxins, emotional state, medical conditions during pregnancy and any use of medication (especially antibiotics).

Maternal medical conditions during pregnancy refer to pre-existing medical conditions, such as thyroid gland related conditions, epilepsy, mental illness, diabetes, heart diseases, hypertension, influenza, urticaria, convulsions, serious anaemia and hepatitis B and conditions induced by pregnancy. The following gestational complications were also considered: edema, severe hyperemesis, threatened abortion, premature rupture of membrane, serious bleeding before delivery (antepartum hemorrhage), placenta previa, vaginal infection or bleeding, fever (temperature >100.4 degree), gestational diabetes, eclampsia and complications caused by malnutrition. A summary binary variable was assigned with value 1 indicating that any of the conditions mentioned above occurred and 0 indicating no any pf the conditions mentioned above occurred.

Risk Factors at Delivery The following risk factors were asked: infant gestational age, wrap of umbilical cord around neck, cesarean delivery, breech birth, and newborn complications such as low birth weight (in grams), delayed crying and abnormal skin color due to hypoxia, apnoea, aspirated pneumonia, intracranial hemorrhage, sclerederma neonatorum, neonatal jaundice, febrile convulsion, congenital malformations, anoxic encephalopathy, congenital rubella, and gastrointestinal diseases. A summary binary variable was assigned with value 1 indicating that any of the conditions mentioned above occurred and 0 indicating no any of the conditions mentioned above occurred.

Statistical Analysis

The quality of the questionnaire was evaluated before data analysis. The software package SPSS 20.0 was used in statistical analysis. Firstly, univariate analysis including *t*-test for continuous data and chi-square test for binary (0/1) or categorical variables were performed for all the potential risk factors to identify those significantly associated with autism. Fisher's exact test was used for factors with frequency <5 in either t case group or control group. Secondly, quick unbiased efficient statistical tree (QUEST) was used to examine the most important variables associated with the risk of autism from the selected variables, in which autism was the dependent variable, while the rest of variables were independent variables. After the most influential factors were selected from the QUEST model, logistic regression analysis was conducted to find the odds ratio (OR) value of each risk factors with control of socioeconomic factors, such as income of family.

RESULTS

A total of 193 autism children aged 3-18 years (average 9.90±4.39 years old) and 733 normal children (9.74±3.73 years old) were included in this study. The case group had 156 males and 37 females with the male to female ratio of 4.2:1; the control group had 590 males and 143 females with the male to female ratio of 4.1:1. Among 1000 questionnaires delivered, 926 were returned and valid. After the univariate analysis, 12 variables were selected from all the potential risk factors (Table 1), including (1) paternal dietary before pregnancy, such as river fish and alcohol; (2) maternal risk exposures during pregnancy, including air conditioner, microwave oven, computer, X-ray, smoking, depression, stressful events and folic acid; (3) risk factors at delivery, such as complications and difficult labor.

QUEST Analysis

The QUEST model (Figure 1) had a total of 3 layers and 8 nodes. The parent node was the use of air conditioner. In the group with air conditioning use, 15.7% of the children had autism, while in the group without air conditioning use, 38.7% of the children had autism, indicating that mothers who did not use air conditioners at home during pregnancy were more likely to have children with autism. For the group using air conditioner during pregnancy, newborn complications were further associated with an increased risk of autism. The group with neonatal jaundice had a higher percentage of autism than those without the condition (40.2% *vs.* 12.3%). For the group using no air conditioner during pregnancy, frequent consumption of freshwater fish of fathers before mothers' pregnancy was associated with a lower risk of autism compared with the group with no paternal freshwater fish consumption (25.4% *vs.* 59.3%). For the group using air conditioner during pregnancy and without newborn complications, the depression of the mothers during pregnancy was related to a higher risk of autism compared to the group with normal pregnant mothers (39.4% *vs.* 10.1%). The synergism of various factors (Figure 2) showed the risk of autism, for example, for the group without newborn complications and depression, but with air conditioner use, the risk of child autism was lowest.

Logistic Regression Results

By unconditional binary logistic regression analysis, the 4 factors identified by QUEST were completely included in the predicted model. The model showed that the following factors were significantly associated with risk of child autism (Table 2): (1) maternal use of air conditioner during pregnancy (OR=0.316, 95% CI=0.22-0.46) and maternal depression (OR=4.822, 95% CI=3.08-7.63); (2) paternal river fish diet before pregnancy (OR=0.383, 95% CI=0.26-0.57); and (3) newborn complications at delivery (OR=4.277, 95% CI= 2.31-7.91).

Table 1. The Variables Selected by Univariate Analysis

Variables	'Yes' /all in Case Group	'Yes'/all in Control Group	Chi-square Value	*P*-Value
Paternal dietary before fertility				
Alcohol	167/193	578/733	18.214	0.000
River fish	36/193	301/733	170.058	0.000
Maternal exposures during pregnancy				
Air condition	113/193	607/733	21.463	0.000
Microwave dove	139/193	395/733	8.515	0.004
Computer	35/193	88/733	6.892	0.009
X-ray	52/193	139/733	9.521	0.002
Smoking	38/193	55/733	30.602	0.000
Stress	5/193	78/733	10.243	0.001
Depression	20/193	49/733	4.464	0.035
Folic acid	39/193	235/733	17.018	0.000
Risk factors at delivery				
Complications	55/193	148/733	9.321	0.002
Difficult labor	56/193	163/733	6.573	0.010

DISCUSSION

Summary of the Study

A well-designed and rigorous case control study, matched by sex and age, was conducted to investigate major environmental risk factors for child autism in China; furthermore, the interaction of multi environmental risk factors was evaluated. The main strengths of this study included: (1) a comprehensive list of environmental risk factors based on our previous study and others' systematic reviews, including the potential environmental exposure of the fathers before mothers' pregnancy, the mothers' routine activities related to exposure, mothers' activities during pregnancy, birth delivery information, and potential exposure during infancy (1st year of baby); (2) the sample size of case group was the biggest in Tianjin so far, which included most of the children and adolescents with autism, at the same time the appropriate controls were selected; (3) the traditional research rule of environmental risk factors for autism was broken-not only the main factors were selected, but also the interaction of different factors were studied by combining QUEST and logistic regression analysis. Finally, our results suggested that the air pollutants, which might either came from out-environment, such as vehicle exhaust, or indoor environment, such as particulate matter, was most important factor (parent node). In addition, the other risk factors should not be neglected, such as paternal river fish diet before pregnancy, maternal depression during pregnancy and newborn complications.

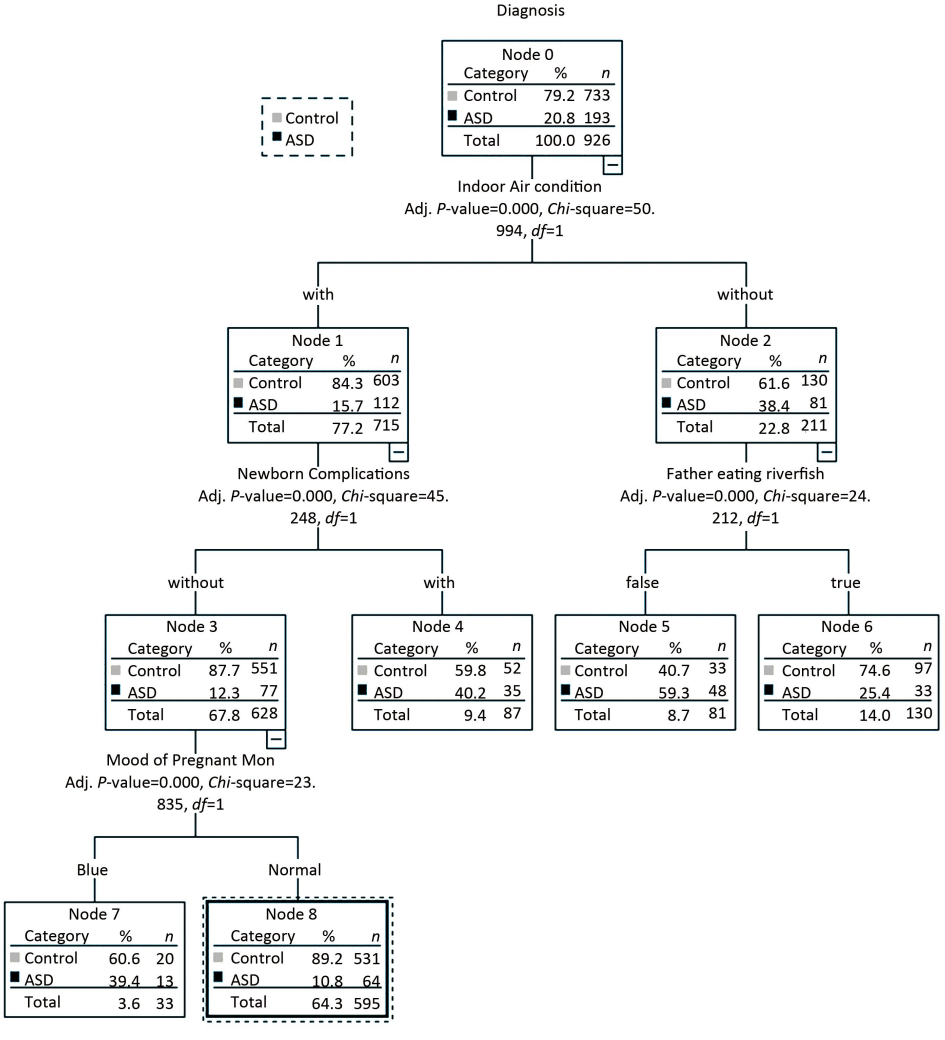

Figure 1. The predicted figure of QUEST for 926 objectives.

Maternal Use of Air Conditioner during Pregnancy

In this study, maternal air conditioner use during pregnancy, a protective factor, was found to be significantly associated with autism, but no previous literature had reported the relationship between air conditioner use and the incidence of autism so far. Air conditioner use might reflect the economic level of the family-in China only the relatively affluent family can afford air conditioning. Thus, it might not be the air conditioner use, but the economic status that contributed to the lower risk of autism. However, based on the fact, the income of family when the infant was born was not found to be associated with autism. Of course, air conditioner use is associated with the season of pregnancy and the season of child birth on the other hand. In Tianjin, most families only use air conditioner in summer (June to August). In this study, 46 autistic children (23.84%) were born in summer, but no season specific statistical significant difference was observed in the number of autism cases (46 in spring, 56 in autumn, and 45 in winter). Obviously, there was no relationship between air conditioner use and the birth season of children, then it was supposed that air conditioner use might be more closely associated with air pollution. The real source of pollution may come from both inside and outside environments. Several studies had explored the association between traffic-related air pollutants (including particulate matter) and autism[25], for example, particulate matter with diameters ≤2.5 μm ($PM_{2.5}$), the maternal exposure to $PM_{2.5}$ during pregnancy was associated with greater odds of child autism[28]. The possible mechanism included oxidative stress and mitochondrial damage[29-30]. The

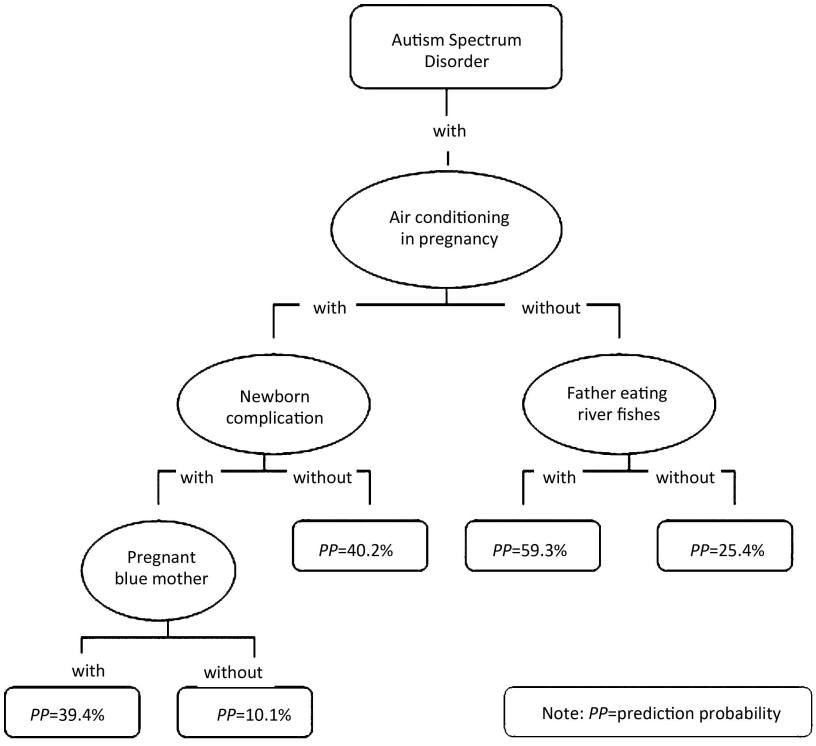

Figure 2. The comprehensive effect of different combinations offactors.

Table 2. The Result of Unconditional Binary Logistic Regression

Name of Variables	B	S.E	*P*	OR	95% CI	
Maternal use of air conditioner	-1.151	0.195	0.000	0.316	0.215	0.463
Paternal river fish diet	-0.961	0.206	0.000	0.383	0.256	0.573
Maternal depression	1.573	0.234	0.000	4.822	3.047	7.631
Newborn complications	1.453	0.314	0.000	4.277	2.314	7.908
Constant	-0.140	0.189	0.459	0.870		

use of air conditioner might reduce the concentration of airborne pollutants resulting from lower airborne particulate matter by filters[31]. Few reports had been found on the association between indoor contaminants and child autism so far. As far as the use of air conditioner was concerned, the possible mechanism of protective effect from similar studies might be that a better controlled indoor environment would reduce damp and conditions that are favorite for microbe growth[32]. So, further studies on association between local air pollution or indoor air population of microbe and child autism are needed to understand the protective effect of air conditioner use.

Paternal Consumption of Freshwater Fish

There is controversy on the recommendation to encourage parents having more fish consumption because fish contains both beneficial nutrients (e.g. high quality protein, vitamin, Omega-3 fatty acids and EPA, DHA)[33] and harmful chemicals that may be neuro-toxicants (e.g. methylmercury)[34]. A number of studies[35-36] reported the beneficial effects of fish diet despite somewhat high mercury concentration. The main mechanism was related to selenium. Fish meat is rich in selenium, which will help fight the adverse effect of mercury by binding to selenium. A Norway study[37] showed that paternal obesity was an independent risk factor for child autism, while a diet with rich fish had a protective effect against fatty liver and obesity by the mechanism of acceleration of mitochondrial fusion process[38]. In other words, the fish diet of fathers might play a role in reducing or preventing paternal obesity. Unfortunately, the fathers' weight was not collected in this study, thus this hypothesis could not be tested. Another possibility is that fish oil might improve the sperm quality, which has been confirmed in a study in rams[39], and another study indicating that the concentration of sperm was increased[40].

Maternal Depression during Pregnancy

Our results also showed that maternal depression was a risk factor to child autism. There have been several studies[41-43] on the association between maternal depression before or in pregnancy and offspring autism, indicating that maternal depression would increase the risk of autism in children. However, in these studies untreated maternal depression was not considered. It was only the maternal exposure to antidepressants, for example, Selective Serotonin Reuptake Inhibitor (SSRI), that had been studied. Thus the possible explanation could be that higher concentration of serotonin caused by antidepressants will influence the neurodevelopment of fetus[44], which might result in autistic behavior and mental retardation. Croen[42] argued that it was too early to make that conclusion, because the potential risks associated with exposure were needed to be balanced with the risks to the mother or fetus suffering from untreated mental health disorders. In this study, we specially investigated the maternal medication (including antidepressants) within two years of the birth of the children to identify the untreated depression of mother. It was not the antidepressants but the mental illness-maternal depression was associated with greater odds of child autism. The molecular biological studies are needed to identify the exact mechanism of this issue.

Neonatal Complications

The neonatal complications were also risk factors for autism in this study, which consisted of neonatal anoxia, jaundice and aspiration pneumonia. However, none of them has shown statistical significance between case and control respectively, so we combined the above three complications into a single variable as neonatal complication, which may represent brain injury of newborn from various causes[45-47]. The possible mechanism of neonatal jaundice was hyperbilirubinemia, which resulted in the damage of the central nervous system, furthermore, leading to hearing loss of newborns[48-49]. Both neonatal anoxia and aspiration pneumonia could result in brain hypoxia, which also could cause hearing loss because of decreased calcium-activated potassium channels[50]. The association between hearing loss and child autism was quite controversial, for no conclusive evidence shows that early hearing loss increased risk of child autism[51-52].

A major weakness of the study was recall bias, which usually exists in case-control study. In the future, we shall establish an effective community cohort to understand the association between environmental risk factors and child autism prospectively.

CONCLUSION

A case-control study by using questionnaire was

conducted to identify the possible risk factors for child autism in Tianjin. By combining a classification tree and logistic regression analysis, maternal depression during pregnancy and neonatal complications were found to be associated with higher risk of child autism, while maternal air conditioner use and paternal freshwater fish dietary before pregnancy were associated with lower risk of child autism.

ACKNOWLEDGMENTS

We greatly appreciate the children and their parents involved in this study, to the supports from the National Natural Science Foundation of China and China Disabled Persons Federation (CDPF) of Tianjin, with their supports, we could conduct this study in the special education schools, contact autistic children and their parents closely, in addition, we also extend thanks to the school doctors and nurses, the parents of both the autistic children and the healthy children, who shared their special experiences with us, the postgraduates participating in this study for study design, data collection, data input and data analysis.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Received: March 4, 2015;
Accepted: July 24, 2015

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