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Highlights

- Although urbanicity generated wealthy and better health care services, it also resulted in stressful social environment, greater social disparities and serious pollution.
- Increased risk for autism with increasing degree of urbanization has been documented in diverse areas, but studies in China are missing.
- Higher level of urbanicity associated with high risk of autism in Chinese children.
- The association of urbanicity and autism in China were only present in male children, not in female children.
- Global urbanization may result in an increased risk of autism.

Journal Pre-proof

Urbanicity and autism of children in China

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Abstract

Objectives: Increased risk of autism with the increment of urbanization has been documented in developed countries. However, very few studies in developing countries focused on this topic. By using Chinese nationally representative large dataset, we investigated the association between urbanicity and autism among children aged 0-17 years in China. Also, we analyzed whether there existed a sexually dimorphic effect on this association.

Methods: Data from the Second National Sample Survey on Disability (SNSSD) was used in this study, and 616,940 children was selected for analysis. Autism was measured by experienced psychiatrists according to The International Statistical Classification of Diseases and Related Health Problems 10th Revision Symptom Checklist for Mental Disorders. Logistic regression models allowing for multiple demographic and socioeconomic covariates were used to evaluate the association between the level of urbanization and autism in children.

Results: Compared with children in low level of urbanization areas, those in high urbanization level areas was 2.12 (95%CI: 1.28, 3.49) times more likely to develop autism, and 1.85(95%CI: 1.21, 2.84) times for those in moderate level of urbanization areas. Stratified analyses found that all observed associations were only in male children, not in female children.

Conclusions: Our findings suggested that higher level of urbanicity was associated with higher risk of autism in children. This association was only present in male children, not in female children.

Keywords: autism, urbanicity, children

Introduction

Urbanization is a major socio-ecological change and progress in human society, mainly taking place at a massive scale in low- and middle-income countries (Lederbogen et al., 2011). Currently, 55% humans live in urban areas, and this proportion will increase to 68% by 2050, with close to 90% of the increase occurring in Asia and Africa regions (Nations, 2018). Although urbanicity generates wealthy, productivity, improved sanitary conditions and better health care services, it also results in stressful social environment, greater social disparities and serious pollution (Dye, 2008; Lederbogen et al., 2011; Li et al., 2016). These factors related to both health benefits and risks, but mental health is negatively affected (Lederbogen et al., 2011). Recently, urbanization has been well-established to increase the risk of mental health problems, which strongly implicated in mood and anxiety disorders, depression and psychosis (McKenzie, Murray, & Booth, 2013; Sundquist, Frank, & Sundquist, 2004; Vassos, Pedersen, Murray, Collier, & Lewis, 2012).

Autism is a neurodevelopmental disorder characterized by social interaction and communication impairments and the restricted and repetitive behaviors (M. B. J. E. c. Lauritsen & psychiatry, 2013). Although the strong genetic aspects in autism etiology have been identified (Miles, 2011), but recent study suggested that environmental factors may have a larger effect on autism (Hallmayer et al., 2011). Of these, increased autism risk with increased degree of urbanization has been found in multiple geographically and ethnically diverse areas (Becker, 2010). For instance, capital city inhabitants in Denmark were found to be two- to three- fold autism risk than their rural counterparts (M. B. Lauritsen et al., 2014). In Japan, higher prevalence of autism was found in city dwellers than in rural residents (Hoshino, Kumashiro, Yashima, Tachibana, & Watanabe, 1982). However, the relationship between urbanicity and autism were rarely concerned in developing countries.

China is leading the largest and unprecedented urbanization around the world. People lived in urban areas increased from 1.72 billion (17.92%) in 1978 to 8.31 billion (59.58%) in 2018, and roughly 260 million urban residents are migrations (Gong et al., 2012; National Statistics Department, 2019). This rapid urbanization accompanied by cities exploding in size and expansion of urban population, which give rise to a lot of problems, such as troubling disparities in health-care access and economic resources, considerable acculturative stress and serious environmental pollution (Gong et al., 2012), and also the increasing risk of mental disorders. Although autism in China is thought to become the leading cause of childhood psychiatric disability with at least 3 million patients (Chinese Mental Health Association Mental Health Branch for the Disabled, 2018), studies about the effect of urbanicity on autism in China are missing.

By using nationally representative large data, we investigated the association between urbanicity and autism in children aged 0-17 years in China. Also, we analyzed whether there

was a sexually dimorphic effect on this association. This study addressed the limitations in previous Chinese studies of urbanicity effect on autism and contributed to the extant literature in developing countries.

Methods

Study population

Data from the Second National Sample Survey on Disability (SNSSD) was used in this study. From 1 April to 31 May 2006, China State Council implemented this national sample survey. The SNSSD database is one of the largest, most representative nationwide population-based data sources in childhood autism and its related disability currently available. The data consist of the recodes of prevalence, causes, severities of disability and socioeconomic status, living conditions, and the health services demand and utilization of disabled persons.

This survey used multistage, stratified random-cluster sampling, with probability proportional to size in 734 counties (districts), 2,980 towns (streets) and 5,964 communities (villages) covering all provincial administrative areas in mainland China. More than 20,000 interviewers, 6,000 doctors of various specialties and 50,000 survey assistants attended this survey. Face-to-face household interview was used to investigate each family member in the selected households. A sample of 2,526,145 non-institutionalized individuals from 771,797 households consented to participate in this survey. More details of SNSSD design and sample processing could be found elsewhere (Zheng et al., 2011). We restricted our analysis to 616,940 children at the ages 17 years old and below who have complete information on autism.

Ethics approval

The survey was conducted in all provinces by the Leading Group of the National Sample Survey on Disability and the National Bureau of Statistics with approval by the State Council of China. All survey respondents provided consent to the Chinese government.

Autism assessment

Autism was identified by using a three steps approach in this study as following: Firstly, mental distress with social function limitations was identified by the screening questionnaire with five items during the household face-to-face interview process. This questionnaire was developed for the survey according to the 'Guidelines and Principles for the Development of Disability Statistics', which had been demonstrated high reliability (Zhang, 2010). Persons who answered a positive response was labeled as likely to be meeting threshold of mental distress with social function limitations. Secondly, psychiatrists who have more than 5 years of clinical experience identified the mental distress with meeting the threshold of mental distress with social function limitations by using The World Health Organization Disability

Assessment Schedule, Version II (WHO DAS II) in persons with possible mental distress with social function limitations (Field et al., 2000). If persons who received a score of 52 or higher were diagnosed as to be meeting the threshold of mental distress with social function limitations. Thirdly, persons who have autism were diagnosed by experienced psychiatrists using The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Symptom Checklist for Mental Disorders (Organization, 1992).

The degree of urbanicity

Participants' addresses were linked to county-level data from 734 counties of 2000 China Census. The degree of urbanicity (urbanization rate) was measured by urbanization rate, representing averages and percentages measured at county level in 2000 China Census.

Measures

The outcome variable was a binary measure (i.e., whether having autism or not). The independent variables were urbanization rate, which was divided into tertiles, representing 'low', 'moderate' and 'high' group areas, to allow the examination of associations with autism. Control variables at the individual levels included age (continuous variable), gender (male or female), ethnicity (minority persons or not), household income per capita (tertile1 (low household income per capita), tertile2 or tertile3 (high household income per capita)).

Statistical analysis

Considering the complex sample design, standard weighting procedures were used to construct sample weights. Population weighted cases and prevalence of autism and their 95% confidence intervals (CIs) by the degree of urbanization were presented in the current study. Logistic regression models allowing for multiple demographic and socioeconomic covariates were used to evaluate the association between the level of urbanization and autism in children, and the odds ratios (ORs) with 95% confidence intervals (CIs) were presented. A P value less than 0.05 was considered statistically significant. The software Stata version 13.0 for Windows (Stata Corp, College Station, TX, USA) was utilized for statistical analysis.

Results

Spatial distributions of the prevalence of autism and urbanization rate by province are presented in Figure 1 and Figure 2. Geographic variation and geographical spatial clustering in the prevalence of autism and the degree of urbanization rate were observed.

Table 1 presents the weighted cases and prevalence of autism by the degree of urbanization rate. Among all children, the lowest prevalence of autism was in the areas with low urbanization rate (1.37 per 10000 children). Prevalence of autism in moderate and high urbanization rate areas were the same (2.80 per 10000 children). Among female children, autism prevalence increased with the increased of urbanization rate, with 1.95, 3.56 and 3.83

per 10000 children in lowest, moderate and highest urbanicity areas, respectively. However, female children reported different variation in the distributions of autism prevalence. For instance, among female children, the prevalence in areas with high urbanization rate was higher than the prevalence in areas with moderate urbanization rate.

Table 2 reports the logistic regression results of urbanization rate and autism. Unadjusted odds ratio in model one revealed that compared with those in low urbanization rate areas, people in areas with high and moderate urbanization rate had more odds of autism, with an Odds Ratio of 1.67(95%CI: 1.10,2.53) and 1.61(95%CI: 1.03,2.52), respectively. After controlling demographic characteristics (Model 2), individuals in areas with higher degree of urbanization were still at greater risk of autism compared with those in lower degree of urbanization areas, with an Odds Ratio of 1.68(95%CI: 1.10,2.57) and 1.79(95%CI: 1.10, 2.91) in high and moderate urbanization rate areas, respectively. Model 3 adjusted for model 2 criteria and socioeconomic conditions, which shows that compared with children in low urbanization rate areas, those in high urbanization rate areas was 2.12 (95%CI: 1.28, 3.49) times more likely to develop autism, and 1.85(95%CI: 1.21,2.84) times for those in moderate urbanization rate areas.

The relationship between the degree of urbanization and autism further tested in the sex specific subgroups. Male children in higher urbanization rate areas have greater likelihood of autism than those in lower urbanization rate areas (high areas: OR=2.13, 95%CI: 1.18, 3.83; moderate areas: OR=1.73, 95%CI: 1.04, 2.88). However, among female children, there was no statistically significant association between the degree of urbanization rate and the risk of autism. More details could be found in Figure 3.

Discussions

The objective of this study was to examine the association between urbanicity and autism in Chinese children aged 18 years old or below, and was to investigate whether there is sex difference in this association. To the best of our knowledge, this is the first study in China to report empirical results of the relationship between urbanicity and autism. The current study demonstrated an association between urbanicity and autism among Chinese children, with a trend towards a higher risk of autism for children in increasing level of urbanization.

The result of children living in higher level urbanicity with greater risk of autism was evidenced in previous researches(Fountain, King, & Bearman, 2011; M. B. Lauritsen et al., 2014; Mandell, Novak, & Zubritsky, 2005). Several hypotheses have been put forward to explain the findings. Firstly, social stress processing hypotheses regards that living or upbringing in high urbanization areas associated with the abnormal amygdala activities(Lederbogen et al., 2011), which may lead to increasing risk of autism(Neuhaus, Beauchaine, & Bernier, 2010). Secondly, immune sensitization hypothesis indicates that immune, autoimmune and inflammatory may play an important role in the relationship

between urbanicity and autism. Living in farming communities and being exposed to by contact with animals can stimulate the immune system of humans, which may have a protective effect on decreasing the risk of autism (M. B. Lauritsen et al., 2014). Thirdly, environmental agents hypotheses suggests that residents in higher urbanization areas correlates with higher risk of pollution agents exposure containing neurotoxic or immunotoxic properties, which increased the risk of autism of children (Kalkbrenner et al., 2010).

Our finding showed that there existed the sex difference in the association between urbanization and autism in children. Living in higher urbanization rate areas increased the risk of autism in male children, not in female children. Sex differences in brain structure and function may be the explanation of this. The cerebral development is relatively slow for males than for females, which lead males to the susceptibility of brain to environmental insults (Insel, Brown, Bresnahan, Schaefer, & Susser, 2005), and this vulnerability may increase the risk of autism in male children. Further, evidence showed that the brain in males than in females is more vulnerable to developmental neurotoxicants exposures (Kern et al., 2017), and some of which are commonly existed in pollution and are more likely to be concentrated in high urbanicity areas. These apparent gender-related neurotoxic effects may also contribute to the sex differences in the association between urbanization and autism. Additionally, socio-culture factors and sample selection bias may contribute to the sex difference. Previous study pointed that some families with children diagnosed with autism may move into higher developed areas with better services and higher rate of urbanization, which may be the reason for increased autism risk in increased urbanization rate areas (M. B. Lauritsen et al., 2014). Due to son preference in Confucian culture society of China, male children than females with autism or developmentally delay often can get more attention and caring from their families, and as a consequence, more male autism children may move to higher urbanicity areas.

Limitations

This study is the first to explore the association between urbanicity and autism in China. Using the dataset coverage across an entire country and more homogeneous samples of autism ascertained by psychiatrists according to the ICD-10, this study enabled us to more precisely estimate the risks of autism, and minimized the information bias which may resulted from diagnostic procedures. However, our study has a number of limitations. First, this study could not test the mechanism of urbanicity role on autism due to the restriction of our survey data. Secondly, some confounders, such as family history of mental illness, could not be controlled in this study, which may lead to a bias to the results. Thirdly, for the measurement of autism in the survey, some autism children without disabilities may not have been identified in this survey. Therefore, these findings may underestimate the overall prevalence of autism.

Conclusions

Our findings suggested that higher level of urbanicity associated with high risk of autism in

children. This association were only present in male children, not in female children. City planners and researchers should do further studies to explore the potential contributors of higher risk of autism in high level of urbanization areas, the reasons of the differences between males and females, and the solutions to mitigate the negative effects of urban living.

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Abstract

Objectives: Increased risk for autism with increasing degree of urbanization has been documented in developed countries. However, less study has focused on this topic in developing countries. By using Chinese nationally representative large data, we investigated the association between urbanicity and autism in children aged 0-17 years in China. Also, we analysis whether there was a sexually dimorphic effect on this association.

Methods: Data from the Second National Sample Survey on Disability (SNSSD) was used in this study, and 616,940 children was selected for analysis. Autism was measured by experiences psychiatrists according to The International Statistical Classification of Diseases and Related Health Problems 10th Revision Symptom Checklist for Mental Disorders. Logistic regression models allowing for multiple demographic and socioeconomic covariate were used to evaluate the association between urbanization rate and autism in children.

Results: Compared with children in lowest urbanization rate areas, those in highest urbanization rate areas was 2.12 (95%CI: 1.28, 3.49) times more likely to develop autism, and 1.85(95%CI: 1.21,2.84) times for those in moderate urbanization rate areas. Stratified analyses found that all observed associations were only in male children, not in female children.

Conclusions: Our findings suggested that higher level of urbanicity associated with high risk of autism in children. This association were only present in male children, not in female children. The findings implicated that global urbanization may result in an increased risk of autism. Further studies are needed to more explore the potential mechanism of urbanicity and autism.

Keywords: autism, urbanicity, children

Author Statement Contributors

Yanan Luo and Lihua Pang contributed equally to this study. Yanan Luo: study concept and design, drafting the manuscript, data analysis and interpretation. Lihua Pang: study concept, critical revision of article for important intellectual content. Chao Guo, Lei Zhang and Yiran Wang: revision of article. Xiaoying Zheng: study concept and design, critical revision of article for important intellectual content. All authors gave final approval of the version to be published.

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Role of the Funding Source

The authors had complete freedom in directing the analysis and reporting the findings, and no editorial direction or censorship was given from any funding agency.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

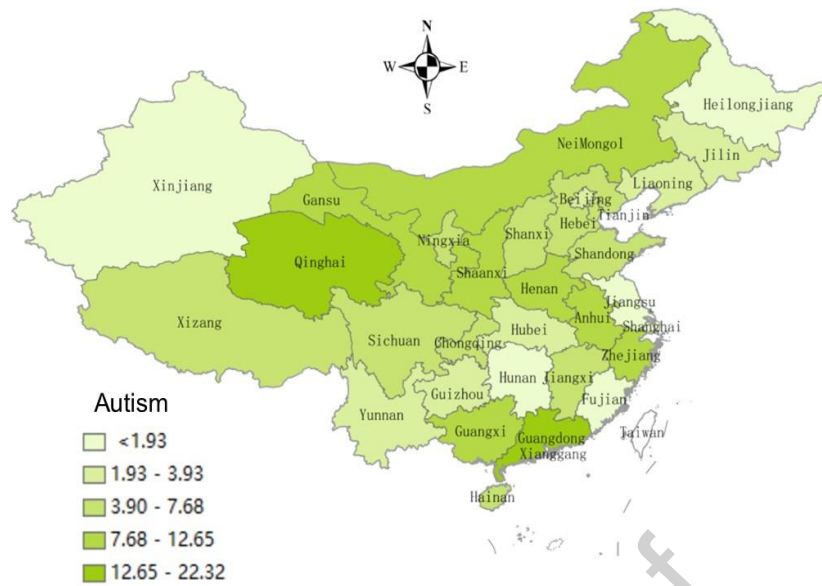


Figure 1. The prevalence of childhood autism by province in China

Note: All prevalence were per 10000 children

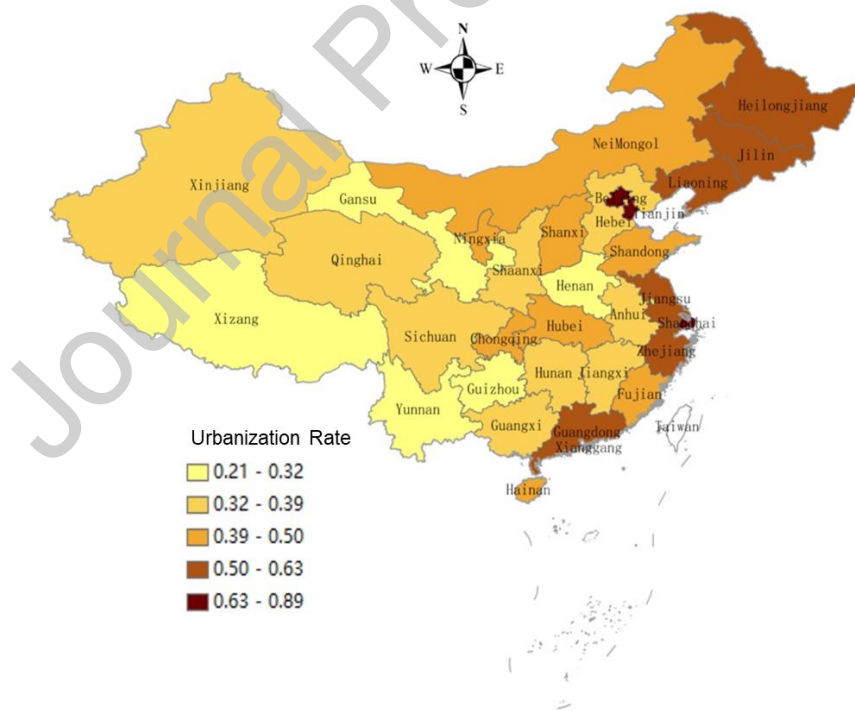


Figure 2. The urbanization rate by province in China

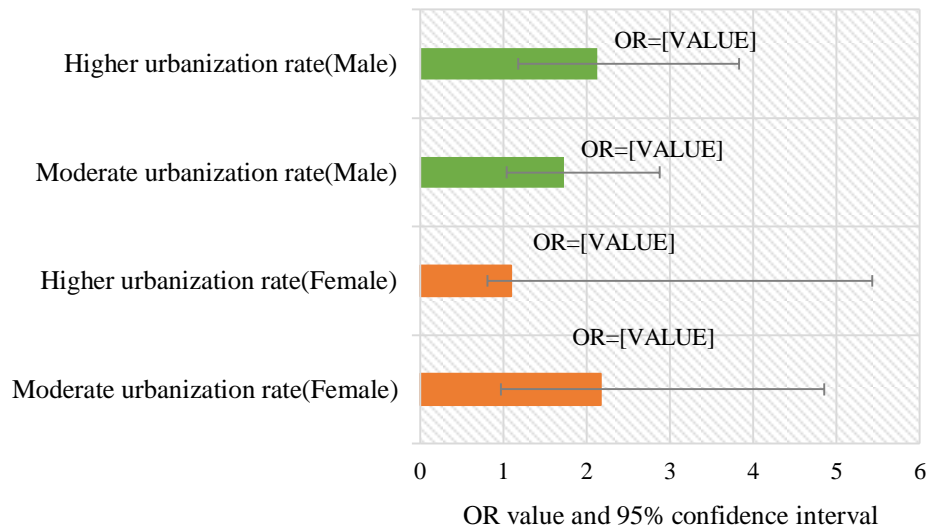


Figure 3. Odds ratio with 95% confidence interval (CI) of the association between urbanization and autism among Chinese children, by males and females

Note: All ORs (95% CI) were adjusted for age, gender, ethnic, residency and household income per capita.

Table 1 Prevalence of autism with 95% confidence interval (CI) by urbanization rate among Chinese children

Characteristics	All children		Male children		Female children	
	Weighted Cases	Weighted Prevalence	Weighted Cases	Weighted Prevalence	Weighted Cases	Weighted Prevalence
Total	77301	2.38(1.92,2.84)	22364	1.49(0.99,1.99)	54937	3.15(2.47,3.83)
Urbanization rate						
Title 1 (Low)	18848	1.37(0.94,2.01)	4557	1.95(1.29,2.94)	14224	0.70(0.29,1.66)
Title 2 (Moderate)	34604	2.80(1.97, 3.99)	10958	3.56(2.53,5.00)	23745	1.81(1.12,2.93)
Title 3 (High)	23849	2.80(1.97,3.99)	68489	3.83(2.57,5.71)	16968	1.65(0.89,3.06)

Note: All prevalence were per 10000 children.

Table 2 Odds ratio with 95% confidence interval (CI) of the association between urbanization and autism among Chinese children

Characteristics	Model 1 ^a	Model 2 ^b	Model 3 ^c
Urbanization rate			
Title 1 (Low)	Reference	Reference	Reference
Title 2 (Moderate)	1.67(1.10,2.53)*	1.68(1.10,2.57)*	1.85(1.21,2.84)**
Title 3 (High)	1.61(1.03,2.52)*	1.79(1.10,2.91)*	2.12(1.28,3.49)**

Note ^a Unadjusted model.

^b Adjusted for model 1 criteria and age, gender, ethnic, residency.

^c Adjusted for model 2 criteria and household income per capita.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$