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The effect of living environment on developmental disorders in cold regions

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Abstract

Developmental disorders (DDs) are a kind of chronic maladies, which can cause serious irreversible detriment to children's physical and mental health. It is predominantly regulated by the interaction of environment and heredity. Cold regions are mainly located in the high latitudes of China. Their living environment is characterized by frequent cold wave, huge temperature difference, severe air pollution, high calorie diet, less exercise, smoking, drinking, *etc*. In recent years, substantial advances have been made in studies of the correlation between the living environment features in cold regions and the DDs. Accordingly, this article reviews the impact of the peculiar living environment of cold regions on DDs, with a view to provide fresh prevention strategies for reducing the morbidity of DDs in China cold regions by ameliorating living environment.

Keywords

developmental disorders; cold region, low temperature; air pollution; lifestyle

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1 Introduction

Developmental disorders (DDs) generally refer to a category of chronic noncommunicable diseases caused by abnormal physical structure and function, which can lead to significant retardation of children's intelligence, physique, cognition, behavior or social adaptation, *etc.*[1-2]. DDs are the fifth leading cause of death among the preschool children worldwide, with the lethal and disabling rates exceeding 80%[3-5]. Conducted to date, the number of children with DDs in the world continues to grow at a rate of 6% yearly, and more than 90% of them comes from developing or economically backward countries[6-7]. In China, the largest developing country in the world, the number of neonates with DDs reaches 900 000 every year, and making up approximately 11% of the world's annual growth rate and ranking among the top three in the world[8-9]. Studies have found that there are conspicuous regional and seasonal differences in DDs[10-11]. The prevalence of certain types of DDs in cold regions is much higher than that in warm regions[12]. Furthermore, compared with that in summer, the morbidity of DDs increased by 7.3% in winter[13].

China is the country with the most widely cross-latitudes, and cold regions account for about 43% of its total land area, including the whole Northeast China and parts of north, northwest and southwest China. According to epidemiological statistics, the incidence of DDs in Northeast China is 40% higher than that in South China[14]. And the prevalence of DDs in North China is three times higher than that in South China[15]. This may be closely related to the unique geographical location, climate characteristics and residents' lifestyle in cold regions. In cold regions, the annual temperature range is broad. Also, winter in cold regions mostly lasts six to eight months with extremely low temperatures, frequent cold wave, short daytime, and long nighttime. In this light, residents in these regions prefer to eat high-glucose high-energy food, excessive cigarette smoking and alcohol drinking, and lack of physical exercises to keep warm. Besides, in winter, most of cold regions utilize coal for heating and power generation, and oil-fueled vehicles are more prevalent, causing much heavier pollution in cold regions than in other regions. A plethora of clinical and animal experiments have indicated that, apart from heredity, high risk factors of living environment such as atmospheric pollution, less exercise, and more smoking and drinking are closely bound up with the occurrence and development of DDs[16-19]. Moreover, environmental factors are more reversible and corrective than genetic factors[20]. Therefore, in an attempt to further enrich and improve prevention strategies and alleviate the prevalence of DDs in cold regions, it is important to elucidate the impact of living environment characteristics of DDs in cold regions.

In this review, we will offer an overview of the types of DDs with high incidence in cold regions and further elaborate the effect of living environment on these DDs.

2 High prevalence of DDs in cold regions

2.1 Autism spectrum disorder

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder, which is originating from early child development and characterized by social dysfunction, narrow interests, mood disorders, repetitive and stereotyped behaviors, *etc.*[21]. According to the latest global ASD burden report, there are more than 28 million ASD patients worldwide. In the preceding three decades, the global prevalence of ASD has increased by 39.3%. Among them, the probability of school-age children suffering from ASD in cold regions is 2.5 times higher than that in tropical regions, and the growth rate of ASD is also growing more speedily than that in tropical regions[22-23]. Additionally, another clinical study involving more than 5.46 million newborns in five countries also confirmed the negative impact of cold ambient environment on the development of ASD. This study found that in the four seasons, the prevalence of ASD was highest in autumn neonates (*i.e.* pregnant in winter)[24]. This may be closely related to the increased risk of virus infection, unbalanced nutrition intake (vitamin D, folic acid, *etc.*), long-term exposure air pollution, and obesity of pregnant women in cold environment[25-28]. Of these, air pollution plays a paramount role in causing ASD. The study revealed that if the concentration of air pollution raised by 5 $\mu g/m^3$, the prevalence of ASD would increase by 7%, in which particulate matter (PM) 2.5 was the most harmful component[29].

2.2 Childhood epilepsy

Childhood epilepsy is a long-term, chronic and paroxysmal nervous system disease that can induce irreversible neuropsychiatric disorder or even death in children, owing to the abnormal spontaneous discharge of brain cell clusters[30-31]. Accreting to statistics, there are 50 million epilepsy patients in the world, of which the proportion of active epilepsy is more than 90%, causing 126 000 deaths per annum[32-33]. And a growing amount of studies have showed that the distribution of epilepsy has distinct territoriality. The prevalence of epilepsy in low latitudes areas is lower, only 1/32 of that in high latitudes areas[34-35]. This may be correlated with the wintry climate factors at high latitudes. The study underscored that the relative risk of epilepsy increased by 1.016 for every 1°C decreased in temperature, and minus 18°C was the best meteorological factor to predict the occurrence of epilepsy[36]. In addition, heavy air pollution, short periods of sunshine, and frequent and excessive alcohol consumption are also the pivotal risk factors for epilepsy in high latitude regions[37-39].

2.3 Congenital heart disease

Congenital heart disease (CHD) is a sort of congenital malformation disease triggered by the anomalous development or formation of heart and great vessels during the embryonic period, which seriously endangers the life and health of infants. It is the overarching reason of death in adolescents and children[40]. Albeit in recent decades, with penetrating into exploration of molecular mechanisms of cardiac development and great advances in cardiac medicine, the global mortality of CHD has descended by 42.7%, its prevalence rate is still 18.7% higher now than before[41-42]. The prevalence of CHD differs among regions, being 2.4 times higher in cold regions than in warm regions[43-44]. Studies discovered that maternal exposure to cold ambient temperature for a long time, combined with upper respiratory infection or body mass index ≥ 30 kg/m^2 was associated with a remarkably increased risk of CHD in offspring (odds ratios [ORs] [95% confidence interval (CI)] of 3.40 [2.05-5.62] and 1.15 [1.07-1.23], respectively)[45-46]. In addition to the aforementioned temperature and obesity, folic acid deficiency and air pollution are also the major factors affecting the high incidence of CHD in cold regions[47-48].

2.4 Cleft lip and palate

Cleft lip and palate (CLP) is a birth defect that can severely influence children's vital physiological functions such as language, breathing, feeding, *etc.* It is also one of the most common craniofacial malformations in newborns, with a global incidence of 0.3/1000[49]. However, under diverse geographic, environmental and socioeconomic circumstances, the prevalence of CLP varies. Studies found that the higher the latitude, the higher the incidence of CLP. For instance, the prevalence of CLP in China is about 2.3-fold than that in Colombia[50-51]. Alternatively, a retrospective study pointed out that the incidence of CLP possesses seasonality, being 69% higher in winter than in summer[52]. On the one hand, this may be due to increased risk of maternal infection by rubella virus during the chilly season[53]. On the other hand, it may be intimately bound up with the unique living environment characteristics in cold regions, such as smoking (active smoking, passive smoking), drinking, medications, air pollution, *etc.*[54-57].

2.5 Congenital hydrocephalus

Congenital hydrocephalus (CH) is one of the most common birth defects in neonates, with a high mortality and disability rates[58]. According to the epidemiological survey, the prevalence of CH in the world is 50/10 000, and the number of CH patients in high latitude countries is about 1.9 times greater than in low latitude countries[59-60]. Researches have suggested the formation of CH is related to many factors, like drinking, virus infection, insufficiency of trace elements (folic acid, vitamin B6, vitamin B12), *etc.*[61]. Studies have found that supplement of trace elements is one of the most sustainable, safe, effective means to prevent offspring from CH during pregnancy. A large population-based cohort study demonstrated that folic acid supplementation can notably attenuate the incidence of CH, especially in cold areas at high latitudes (OR 0.29, 95% CI 0.12-0.69)[62] (Table 1).

3 The effect of living environment on DD diseases in cold regions

3.1 Air pollution

Air pollutants can be divided into the following categories: PM, heavy metals, organic components, or gas pollutants, which can badly impair the healthy growth and development of children. PM refers to liquid or solid particles suspended in the air. For one thing, PM can directly enter the cerebrum through the blood-brain barrier or olfactory nerve to affect the development of body[63]. For another, PM can affect the signals of gut-brain axis by altering gastrointestinal microorganisms, increasing tryptophan metabolites, dampening the expression of anti-inflammatory factors, thus indirectly jeopardizing the growth of organism[64]. A quantity of studies had detected that per 10 μg/m^3 increment in PM would give rise to an increase of 10%-19% in the number of children with DDs, of which the first trimester is the most susceptible (adjusted odds ratio [aOR] 1.21, 95% CI 1.03-1.42)[65-68]. Additionally, heavy metals, organic components and gas pollutants can also impact the normal growth of body by hindering the migration of neurons, inhibiting the formation of synapses, interfering the transmission of neurotransmitters, and altering gene expression profiles, respectively[69-70]. A retrospective cohort study from the state of Florida revealed that if gravidas were exposed to a high concentration of heavy metals environment for a long period of time, the prevalence of DDs in their offspring could raise by 24%[71]. Wang *et al.* found that gas pollutants such as nitrogen dioxide (NO_2) and carbon monoxide (CO) could influence the whole pregnancy and markedly add to the danger of neonatal DDs through a random-sample survey of 1 million people, hazard ratios (95% CI) of 1.39 (1.22-1.58) and 1.93 (1.55-2.39), respectively. But no relevancy between sulfur dioxide (SO_2) and DDs was detected in this study[72]. Nevertheless, another large-sample population-based cohort study noted that SO_2 could increase the risk of DDs in neonates (OR 1.36, 95% CI 1.14-2.48), yet no noticeable correlation has been traced between NO_2 and DDs[73]. This heterogeneity may be relevant to the concentration of pollutants and the exposure time in different regions.

Table 1 Representative studies on proving high prevalence of DDs in cold regions

DDs	References	Country	Number in study	Purposes	Conclusions
ASD	Sun *et al.*[23]	Jilin, China Shenzhen, China	20 000 children	To determin the prevalence of ASD in children in Jilin and Shenzhen	The prevalence of ASD in school-age children in Jilin and Shenzhen was 108 per 10 000 and 42 per 10 000, respectively
Epilepsy	Zheng *et al.*[34]	Hainan Province of China	16 676 participants	To assess the epidemiological characteristics of epilepsy in the tropical rural areas of Hainan Province of China	The prevalence of epilepsy in the tropical rural areas of Hainan Province of China was 0.24 per 1 000
Epilepsy	Syvertsen *et al.*[35]	Nordic countries	The article included 38 original articles.	To conduct an evidence-based assessment of the prevalence of epilepsy in Nordic countries	The highest prevalence of epilepsy in Nordic countries was 7.6 per 1 000
CHD	Liu *et al.*[43]	Xinjiang, China	14 530 school-age children	To evaluate the prevalence of CHD in Xinjiang, China	The prevalence of CHD in Xinjiang was 16.5 per 1 000
CHD	Han *et al.*[44]	Southwest China	244 023 children	To collect epidemiological data of CHD in school children in southwest China	The prevalence of CHD in children in southwest China was 6.9 per 1 000
CLP	Zhu *et al.*[50]	Guangdong Province, China	7 134 693 infants	To explore the temporal and spatial distribution of CLP	The prevalence of CLP in infants in Guangdong province was 7.55 per 10 000
CLP	Alonso *et al.*[51]	Colombia	15 225 participants	To estimate the prevalence of CLP in Columbia from 2009 to 2017	The prevalence of CLP in Columbia was 3.27 per 10 000
CH	Tamber *et al.*[59]	-	Data from the WHO-affiliated ICBDSR	To review the epidemiology of CH in infants	The prevalence of CH in India was 10.4 per 10 000
CH	Liu *et al.*[60]	China	176 223 livebirths	To evaluate the epidemiology of CH in China	The prevalence of CH in China was 20.3 per 10 000

DDs, developmental disorders; ASD, autism spectrum disorder; CHD, congenital heart disease; CLP, cleft lip and palate; CH, congenital hydrocephalus; WHO, World Health Organization; ICBDSR, International Clearinghouse for Birth Defects Surveillance and Research.

The bulk of cold regions are located in remote areas, and the majority of them are heavy industrial and agricultural bases. Furthermore, the life-style of coal combustion for heating and crop residue burning all led to a striking higher pollution level in cold regions than that in other districts. Accordingly, cold regions are high incidence localities of CLP, CHD, ASD, or other DDs.

3.2 Diet, exercise

For the sake of guaranteeing adequate caloric supplement, inhabitants in cold regions held a lifestyle of eating high sugar, high salt, and high animal fat diet and neglecting exercise. Hence, there is a high prevalence of gestational diabetes mellitus (GBM) and gestational hypertension in these regions. As of five-month is the momentous period for the growth and development of fetal organs. Hypertension eclampsia and the intrauterine high-glucose environment caused by GBM, on the one hand, can result in placenta ischemia due to spiral artery remodeling, defects of trophoblastic infiltration, microvascular stenosis, *etc.*, thereby impacting the development of the fetus[74-75]. On the other hand, they can also further augment the susceptibility of fetal morbid development by activating inflammatory response and oxidative stress *in vivo*[76]. However, exercise can promote angiogenesis, enhance the delivery of oxygen and the metabolism of nutrients to maintain the health status of children. Researches have pointed out that GBM and gestational hypertension can exacerbate the hazards of children DDs by 4.2-fold and 1.9-fold, respectively[77-78]. Another study further indicated that if gravida suffered from both GBM and gestational hypertension simultaneously, the risk of neonatal DDs would be far greater (OR 6.56, 95% CI 4.46-9.65)[79]. Tana *et al.* reported that compared with the control group, exercise reduced the prevalence of the DDs in the offspring of GBD mice by 34.5%[80]. Addition to exercise, intaking trace elements is also one of the available approaches to prevent DDs[81-83]. This is owing to the pivotal role of trace elements in retaining redox homeostasis and regulating signal transduction pathways and immune function in healthy growth and development of body[84]. But the dietary structure of inhabitants in cold regions is relatively unitary, and the supplement of trace elements is often ignored. Therefore, this may also be one of the critical causes for which children in cold regions are prone to certain DDs, such as ASD, CHD, CH, *etc.*

3.3 Smoking, alcohol

Smoking is one of the cardinal sources of indoor air pollution in cold regions. The study has found that smoking in first-trimester can raise the risk of DDs (relative risk 1.1, 95% CI 1.1-1.2). And even if smoking cessation before pregnancy, it can still augment the prevalence of DDs by 40%[85]. Also, another case-control research pointed out that if maternal passively contacted smoking environment three times a week, the danger of neonatal DDs would increase by 2.75-fold[86]. However, which has the most sizable impact on DDs, active smoking or passive smoking, remains disputable[87-88]. There are multitudinous chemical components in smoke, including nicotine, formaldehyde, acetone, CO, *etc.* On the one side, they can reduce the oxygen supply to the fetus. On the other side, they can down-regulate the expression of noggin protein and bone morphogenetic protein-2, and then impel the formation of related DDs, such as ASD, CLP, *etc.*[89].

The alcohol exposure of newborns in cold regions is obviously higher than in other regions due to the perennial frigid ambient. Luderer *et al.* discovered that alcohol raised the prevalence of DDs by 20%[90]. Katrine *et al.* also validated that heavy prenatal alcohol exposure conferred the added risk of DDs (prevalence ratio 1.38, 95% CI 0.83-2.28)[91]. Alcohol is a latent teratogen. First, alcohol can enhance the expression of nitric oxide (NO) synthase to generate excessive NO and produce neurotoxicity affecting the neural development of embryos[92]. Second, alcohol can hinder the expression of bone morphogenetic protein, interfere the retinoic acid and Wnt/β-catenin signaling pathways, *etc.*, whereby inducing apoptosis and functional defects of cardiac neural crest cells[93]. So the unrestrained drinking lifestyle of the residents in cold regions is one of the causes for the high morbidity rates of epilepsy, CLP, CHD in children.

3.4 Low temperature

Winter in cold regions is the high incidence season of virus infection, for its low temperature and long duration. Virus infection is corresponding with the occurrence of various DDs. A population-based cohort study demonstrated that the hazard of fetal DDs in cytomegalovirus infection pregnancy women was 233-fold higher than that in on-infected ones[94]. Another report on the burden of TORCH (Toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex virus) infection in newborns from China indicated that roughly 86% of rubella infected fetuses were accompanied by DD of cardiovascular system[95]. Some drugs used for anti-infection treatment (such as fluoroquinolones, tetracyclines, *etc.*) can also impede the normal growth and development of fetal systems[96]. This may be due to the fact that viruses can up-regulate the levels of pro-inflammatory factors and directly curb the growth and differentiation of embryonic mesenchymal cells[97]. Moreover, when Zhu *et al.* explored the impact of long-term cold exposure on the regulation of central energy balance in mice, they found that long-term cold exposure could damage the glucose homeostasis of body by upregulating the expression of orexigenic peptides in the central amygdala and attenuating the activity of an orexigenic brain-derived neurotropic factor in the ventromedial hypothalamic nucleus[98]. Hence, persistent low temperature in cold regions may be a critical catalyst to accelerate the occurrence of DDs induced by viral infection and GBM (Fig. 1).

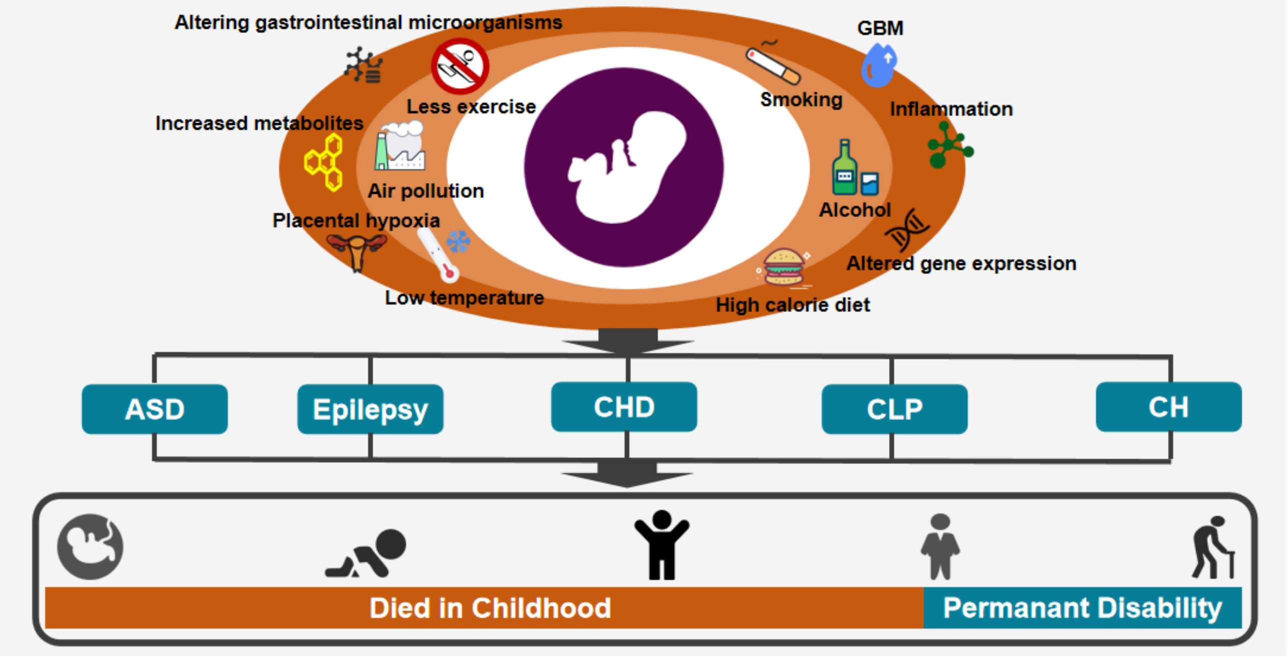

Fig. 1 The effect of living environment on DDs in cold regions

ASD, autism spectrum disorder; CHD, congenital heart disease; CLP, cleft lip and palate; CH, congenital hydrocephalus; GBM, gestational diabetes mellitus.

4 Conclusion

The diversity of living environment traits is one of the pivotal factors resulting in the high prevalence of some DDs in cold regions of China. Despite in recent years, multitudinous advances have been made in exploring the correlation between the inherent characteristics of the living environment in cold regions and DDs. Nevertheless, compared with the extensive and in-depth research on genetic mechanisms of DDs, the exploration of environmental factors is still in its infancy. And studies on the linkage between environmental and genetic factors in the regulation of DDs are also deficient. Therefore, the current approaches and measures of DD prevention and control are mostly restricted to gene screening and treatment, ignoring the plasticity of environmental elements in DDs. So, in order to formulate efficacious prevention and control strategies which can alleviate the disease burden of DDs in cold regions of China. Clearly, large-scale cohort studies, the establishment of animal disease models, and pathophysiological experiments are needed for future studies to further explore the impact of environmental factors of cold regions on the occurrence and development of DDs.

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Conflicts of interests

Wang Y C is an Editorial Board Member of the journal. The article was subjected to the journal's standard procedures, with peer review handled independently of this member and his research groups.

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