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High prevalence of congenital heart disease at high altitudes in Tibet

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Abstract

Background: Previous small sample studies suggested that elevated altitudes might be associated with the incidence of cardiovascular diseases. However, it remains uncertain whether high altitudes (over 3000 m above sea level) are related to congenital heart disease. We therefore explored the prevalence of congenital heart disease in a large cohort of students in the world's largest prefecture-level city with the highest altitude.

Methods: This cross-sectional study included 84,302 student participants (boys 52.12%, girls 47.88%, with an average age of 10.62 ± 3.33 years). Data were extracted from the screening results among different altitude area schools in Nagqu from June 2016 to August 2017. Students were first screened by performing a physical examination consisting of cardiac auscultations and clinical manifestation screenings. An echocardiography was performed to confirm and identify the subtype of congenital heart disease.

Results: The prevalence of congenital heart disease among students in Nagqu, Tibet, was 5.21‰ (439 cases). The most common congenital heart disease type was patent ductus arteriosus, representing 66.3% of congenital heart diseases diagnosed in this study, followed by atrial septal defect and ventricular septal defect, representing 20.3% and 9.1% of congenital heart diseases, respectively. Students living in higher altitudes were significantly more prone to have congenital heart disease than students in locations with lower altitudes. The prevalence of congenital heart disease in girls was found to be higher than that of boys.

Conclusions: The correlation between congenital heart disease and increased altitude is noteworthy. This study's results are the first big data epidemiological investigation to confirm that high altitude is a significant environmental risk factor for congenital heart disease, especially patent ductus arteriosus. Furthermore, the results provide additional support to make a diagnostic and treatment plan to prevent congenital heart disease in high altitude areas.

Keywords
Congenital heart disease, high altitude, prevalence, environmental risk factor

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Introduction and aims

Congenital heart disease (CHD) is one of the most common congenital defects and accounts for approximately one-third of congenital defects worldwide, representing severe global health issues.[1,2] The relationship of CHD to genetic and environmental factors has not been dealt with in depth. Previous works have failed to provide consistent evidence to address the relationship between high altitudes and CHD. Despite a great deal of interest, we believe that this is the first study performed in an actual high altitude area (above 2500 m). Due to the limiting of industrialisation in high altitude areas, the environment (air, soil, water

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and foods) rarely becomes polluted, therefore the decreased barometer pressure leading to an environmental low oxygen pressure would be considered as the single risk factor, which could be regarded as a factor to aggravate the condition of all types of cardiovascular illness, such as CHD.[3] Knowing about the prevalence of CHD in high altitude areas would provide additional preventive and therapeutic methods for those diseases.

Nagqu, Tibet, is considered to be the best candidate research area because the average altitude in the area is 4000 m. It is the world's largest city by land area, and covers an area of 450,537 km^2 with a population of 462,381 (as of the 2010 census).[4] Nagqu is also considered the least developed area of the world. The economy aggregate and gross domestic product per capita of the area are lower than the least developed country in the world.[5] Combined with Nagqu's abundant characteristics information, this CHD epidemiological investigation would help to understand better the prevalence of CHD in this area so that a comprehensive health management plan could be developed to prevent CHD in high altitude areas.

Study design and methods

The ethics committee of Tibetan Fu Kang Hospital in Tibet's autonomous region approved the study (approval number 01602) and written informed consent was obtained from the guardians of the children. The study design, CHD diagnosis, inclusion and exclusion criteria, patients' population, data collection and data analysis are described in the Supplementary methods section.

Results

Study population

This study recruited a total number of 84,302 students in Nagqu prefecture, including 43,935 boys (52.12%) and 40,367 girls (47.88%). Among them, 439 students (median age 10.62 ± 3.33 years) were diagnosed with CHD after the screening, consisting of 271 girls and 168 boys.

CHD prevalence at different altitudes

A total number of 84,302 students from 12 counties, which had diverse altitudes, were included in this study. Table 1 demonstrates significant differences ($P < 0.001$) of CHD prevalence at different altitudes, a total number of 439 students were diagnosed with CHD. This result strengthened the positive correlation between CHD prevalence and high-altitude locations (see Figure 1).

Subtypes of CHD and constituent ratios

The pathogenesis of different subtypes of CHD is different. The most common type of CHD was found to be patent ductus arteriosus (PDA), with 291 (66.3%)

Table 1. The prevalence of CHD in each county and area.

Altitude (m)	Country	Investigate students ($N = 84,302$)	Diagnosed with CHD ($N = 439$)	Prevalence for country (‰)*[a]	Prevalence for altitude (‰)*[b]
3500–4000	Biru	10,426	30	**2.88**	**2.26**
	Suoxian	8548	14	**1.64**	
4001–4500	Baqing	7816	26	**3.33**	**5.18**
	Jiali	5832	49	**8.40**	
	Nagqu county	11,240	62	**5.52**	
	Nagqu area	11,889	41	**3.45**	
>4500	Nierong	5759	22	**3.82**	**8.12**
	Bange	5632	38	**6.75**	
	Anduo	6134	73	**11.90**	
	Shenzha	3846	20	**5.20**	
	Nima	5038	33	**6.55**	
	Shuanghu	2142	31	**14.47**	

CHD: congenital heart disease.
[a]Negative binomial regression.
[b]Chi square test, $\chi^2 = 33.86$.
*$P < 0.001$.

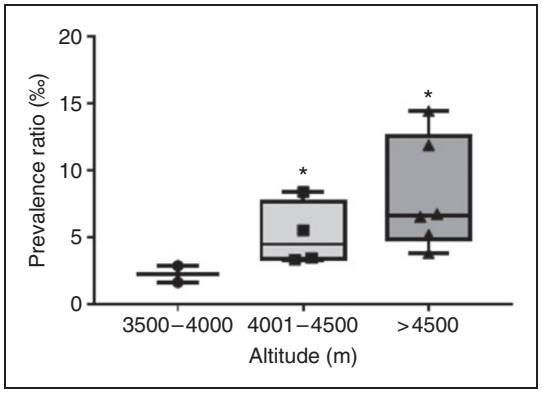

Figure 1. Prevalence of congenital heart disease in three high altitude areas. The prevalence was consistently increased as the altitude becomes higher, $*P < 0.001$.

Table 2. Subtypes of CHD and constituent ratio.

Subtypes of CHD	Cases (*n*)	Constituent ratio (%)
PDA	291	66.3
ASD	89	20.3
VSD	40	9.1
ASD with PDA	5	1.1
Aortic stenosis	4	0.9
ASD with VSD	3	0.7
VSD with PDA	2	0.5
Aortic coarctation	1	0.2
Mitral valve prolapses	1	0.2
Pulmonary stenosis	1	0.2
Tetralogy of Fallot	1	0.2
Single ventricle heart defects	1	0.2

CHD: congenital heart disease; PDA: patent ductus arteriosus; ASD: atrial septal defect; VSD: ventricular septal defect.

cases being diagnosed, followed by atrial septal defect (ASD) in 89 (20.3%) cases and ventricular septal defect (VSD) in 40 (9.1%) cases. Detailed information is shown in Table 2.

CHD prevalence by subjects' gender

In the 439 confirmed CHD cases, 271 of them were girls, with a prevalence of 6.71‰. Only 168 boys were diagnosed with CHD, with a prevalence ratio of 3.82‰. The prevalence of CHD in girls is higher than in boys, and the difference is statistically significant (6.71‰ vs. 3.82‰, $P < 0.001$) (see Table 3). The male-to-female ratio of CHD prevalence in different altitudes was 18:26 (3500–4000 m); 63:115 (4001–4500 m); and 85:132 (>4500 m), respectively ($\chi^2 = 33.91$, $P < 0.001$).

Table 3. The prevalence of CHD by genders.

Altitude (m)	Boys	Girls
3500–4000	18	26
4001–4500	63	115
4501–5000	85	132
Total	168	271

CHD: congenital heart disease.
$\chi^2 = 33.91$.
$P < 0.001$.

Discussion

CHD has been described as a leading cause of death in infancy and childhood, and represents a significant public health issue.[2] The low heritability indicates that the environmental factors, such as the altitude and industrialisation, rather than genetic factors, would play the most critical role in the incidence of CHD.[6] The combined effects of the low oxygen partial pressure and high pulmonary vascular resistance, higher central systolic blood pressure and increased arterial stiffness, while in the hypoxic environment at high altitudes, causes delayed defect closure or even failure to close, which predisposes patients to premature heart failure.[7,8]

The best diagnosis and treatment window for CHD is before the primary pulmonary hypertension generated after birth. Therefore, screening for preschoolers, toddlers and infants is urgently needed to improve the health condition of younger children with CHD.

Conclusions

The correlation between CHD and the increased altitude is noteworthy. This study's results are the first big data epidemiological investigation to confirm that high altitude is a significant environmental risk factor for CHD, especially PDA. Furthermore, the results provide additional support to make a diagnostic and treatment plan to prevent CHD in high altitude areas.

Declaration of conflicting interests

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