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ORIGINAL ARTICLE

Differences by Altitude in the Frequency of Congenital Heart Defects in Colombia

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Abstract More evidence is needed that links the diagnosis of different congenital heart diseases (CHD) identified after birth, with intermediate altitudes above sea level in geographically and ethnically diverse populations. Our aim was to estimate relative frequencies of CHD diagnosis by altitude and gender in the pediatric population of 12 cities in Colombia. This was a cross-sectional study based on the information collected between 2008 and 2013 in Colombia, during annual congenital heart disease (CHD) case detection campaigns in the post-natal period. All children underwent physical examination, pulse-oximetry, and echocardiography. The odds ratio (OR) was used as the summary statistic to assess associations with altitude in the relative frequency of CHD diagnosis. Data from 5900 children who attended the campaigns were evaluated (54.3 % male), out of which 3309 (56.1 %) were diagnosed with CHD. There were statistically significant differences in the relative distribution of the different CHD by city altitude and gender ($p < 0.0001$). When compared with sea level, altitudes between 1285 and 3000 m above sea level were associated with increased Patent Ductus Arteriosus (PDA) (ORmh 1.68, 95 % CI 1.34–2.09; $p < 0.0001$) and left ventricular outflow tract obstruction (LVOTO) diagnoses (ORmh 2.06, 95 % CI 1.63–2.61; $p < 0.0001$), while the opposite was true for right ventricular outflow tract (RVOTO) diagnosis (OR 0.60; 95 % CI 0.49–0.74, $p < 0.0001$). These associations were not modified by gender differences. In a geographically and ethnically diverse population, altitudes between 1285 and 3000 m above sea level carried an independent and clinically important excess diagnostic risk of PDA and of LVOTO, when compared to all other CHD.

Keywords Congenital heart disease · Prevalence · Altitude · Andean region

Abbreviations

CHD	Congenital heart disease
VSD	Ventricular septal defect
RVOTO	Right ventricular outflow track obstruction
ASD	Auricular septal defect
PDA	Patent Ductus Arteriosus
LVOTO	Left ventricular outflow track obstruction
m.a.s.l	Meters above sea level
kg	Kilograms
cms	Centimeters
OR	Odds ratio

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Introduction

Congenital heart disease (CHD) is a result of alterations of multifactorial origin that are thought to occur predominantly in the pre-natal period, where genetic and environmental factors interact [1, 2]. Due to this, CHD has significant geographic and ethnic variability, and the largest burden is present in low and middle-income countries [3, 4]. Although the multifactorial origin of CHD has been a very active research area worldwide, efforts have mainly focused on the role of genetic determinants of heart defects [5].

The role of high altitude above sea level as an environmental determinant of CHD has been postulated for the past 60 years through different mechanisms, including embryonic tissue hypoxia [6] or even as a risk factor that operates at the time of delivery at high altitude, as may be the case for Patent Ductus Arteriosus (PDA) or atrial septal defect (ASD, that could be related more to the persistence of pulmonary hypertension than a congenital defect). While some cases of PDA may be predominantly associated with genetic and other prenatal factors [7, 8], its increased frequency at high altitudes clearly suggest a leading role for environmental mechanisms mediated by low atmospheric pressure and the persistence of pulmonary hypertension after birth [9, 10].

Reports of excessive occurrence of PDA at high altitudes have been published since the 1950s [11, 12]. Unfortunately, the evidence that supports this association has limitations: It has been mostly derived from case reports or prevalence estimates with questionable denominators and from a limited number of sites [11–19]; has been derived mostly at altitudes well over 3000 m [11, 13, 14, 16–19]; is based on limited PDA case numbers [11, 14, 15]; has not taken into account gender differences in PDA occurrence [10, 14–17]; has not compared PDA diagnosis frequency against other CHD [11, 12, 18]; or has been more frequently reported in isolated populations with relatively homogenous geographical and ethnic backgrounds [11, 13–19]. The clinical and epidemiological association between other CHD and altitude is even less clear [14, 16, 19].

Colombia is inhabited by 48 million people, located in the northern section of South America between the Pacific and Atlantic Oceans with an area of 1,141,748 km^2 [20, 21], and is one of the most geographically and ethnically diverse countries in the world [22], with over 80 different ethnic groups [23]. Colombia is about 40 % mountainous, with a mostly urban population (70 %) mainly distributed in the Andean and Caribbean regions. While altitudes range from sea level to 6000 m, the most densely populated regions are below 3000 m, with more than 14 million inhabitants living at altitudes between 1000 and 2600 m above sea level.

Our institution in Bogota has funded a social program in different Colombian regions for the past 20 years, aimed at the detection and treatment of postnatal CHD cases in children. For this, a group of pediatric cardiologists and volunteers travel annually in a systematic fashion to 12 geographically and ethnically diverse Colombian cities with a range of altitudes between sea level and 2800 m and a combined catchment population of over 5 million inhabitants, to conduct uniform campaigns for CHD case detection. The population studied in the campaigns can be a multifactorial model of the risk of occurrence of CHD. In this multifactorial model, one of the most important variables is altitude. Based on the information collected in the last 6 years of the campaigns, the objective of the current study was to put to test the association of PDA and other CHD with intermediate altitudes in Colombia, and to evaluate whether gender differences modify these associations.

Methods

We conducted a cross-sectional study using the database of the campaigns conducted in 11 provinces (12 cities). For uniformity of information collection and reporting, to attenuate potential differences over time in case mix due to migration in what are very dynamic social groups, in industrialization and other physical factors within and between cities [24], and given that diagnostic criteria of CHD may show changes over time [25], we limit this report to the last 6 years of the campaigns (2008–2013).

The campaigns have kept close adherence to the methodology for case detection and physical examination over the years; they have been conducted on an annual basis and almost always on the same months. In each city, an open call for probable CHD cases is done 3 months in advance and spread through local media/information channels as well as with support from local authority, civil society and religious groups.

During the actual campaign, demographic and health data are collected on each new attendee, a physical examination focused on vital signs and on the presence of signs and symptoms of CHD is performed, and pulse-oximetry and electrocardiogram data are collected. After these procedures, a diagnostic echocardiogram (SonoSite Edge, series 03wl05) by a pediatric cardiologist with experience in CHD is performed. All new CHD cases detected are then stratified by severity, and a triage process is carried out, and if pertinent the child and a responsible adult are transported to FCI-IC in Bogotá for further study

Table 1 City characteristics of CHD case detection campaigns in Colombia, 2008–2013

Cities[a]	Population (inhabitants 2015)	Altitude (m.a.s.l)	Detection campaigns during study period	N	CHD *n* (%)
Tunja	118,380	2822	2	253	104 (41.1)
Duitama	112,692	2530	3	330	144 (43.6)
Pasto	440,040	2527	5	1041	485 (46.5)
Manizales	396,075	2200	6	664	348 (52.4)
Ibagué	553,524	1285	1	133	68 (51.1)
Villavicencio	484,471	467	3	225	124 (55.1)
Yopal	193,736	390	3	342	108 (31.5)
Cúcuta	650,011	309	6	626	309 (49.3)
Valledupar	453,205	168	1	144	86 (59.7)
Montería	441,301	18	6	703	506 (71.9)
Barranquilla	1,218,475	18	6	760	506 (66.5)
Cartagena	1,001,755	2	6	679	521 (76.7)

m.a.s.l meters above sea level, *N* children evaluated, *CHD* congenital heart disease

[a] Cities appear in order of altitude, from highest to lowest

and treatment, including heart catheterization and heart surgery if clinically appropriate.

For this study we included data on all attendees less than 18 years of age that presented signs or symptoms of heart disease such as heart murmurs, stunting, syncope, breathlessness or sleep complains, cyanosis, family history of CHD or un-explained deaths before 40 years of age. We did not exclude data from children based on genetic syndromes, or other extra-cardiac abnormalities. Data from patients with premature birth were excluded.

Data Collection and Information Sources

The campaigns keep a systematic registry of all subjects evaluated and diagnosed with CHD. The registry was used to identify all subjects studied between 2008 and 2013. All duplicate records on children seen more than once in the campaigns were excluded. The diagnosis of CHD for each case, for both isolated and syndromic defects followed a uniform classification procedure [26], without knowledge of origin. In patients with complex CHD the main diagnosis was taken (for example, in a Tetralogy of Fallot with ductus arteriosus, or in a d-Transposition of the great arteries with ventricular septal defect, the diagnosis taken was that of Tetralogy of Fallot and d-Transposition, respectively).

Statistical Analysis

Descriptive statistics such as proportions and percentages were used for categorical variables such as gender and type of CHD. Continuous variables such as age, weight, and height used median and interquartile range (IQR). The relative frequency of the different types of CHD is expressed as percentages, by city altitude and by gender. The Chi-square probability density function was used to evaluate overall differences in type of CHD by city of diagnosis.

To test the hypothesis of differences in diagnosis by exposure to altitude above sea level, CHD data from the five cities above 1000 m were grouped and compared with grouped data from the seven cities below 500 m.

The odds ratio (OR) was used as the summary statistic to assess differences in the relative frequency of each CHD (when compared with all other CHD) by low or intermediate altitude. Initially a crude OR was computed, and the Chi-square probability density distribution was used to test for statistical significance. The data were then stratified on gender, and the Mantel–Haenzel weighted OR (Rmh) and Chi-statistic were used to obtain a summary statistic across the strata, to test for significance of the association, and to calculate confidence intervals (CIs) for the OR. A test for homogeneity was calculated to assess the appropriateness of obtaining an adjusted OR across gender strata [27]. Due to multiple statistical comparisons, the null hypothesis of no association was rejected with p values equal or less than 0.01. Analyses were conducted in SPSS version 18 and Epidat 4.1 software.

The study procedures were approved by FCI-IC Institutional Review Board.

Results

The 12 cities visited, with population, altitude, and number of children detected and diagnosed with CHD, are shown in Table 1. Between 2008 and 2013, 5900 children were

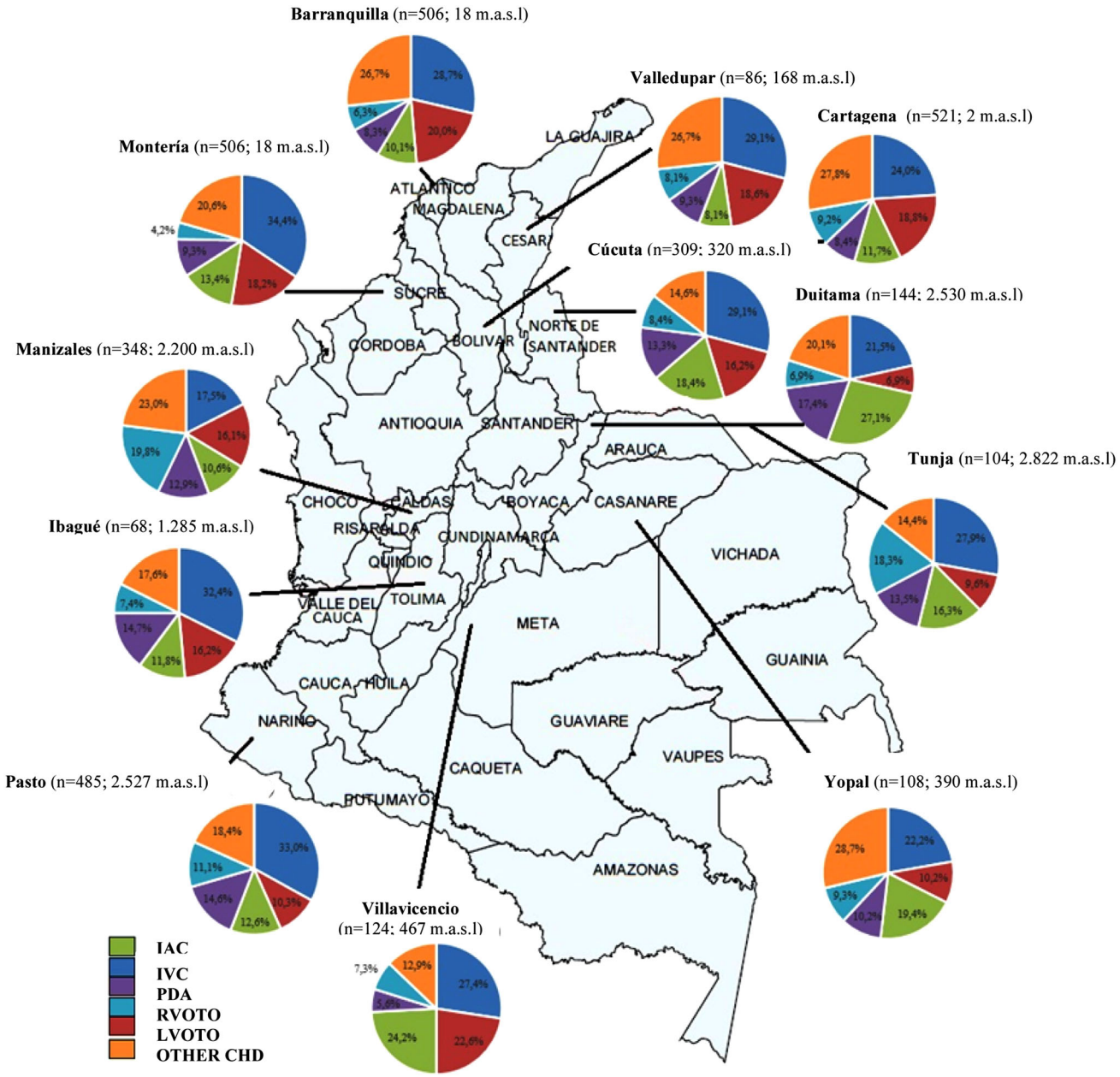

Fig. 1 Distribution of congenital heart disease by city of diagnosis. Colombia, 2008–2013

evaluated. 54.3 % were male, and median age, weight, and height were 7 years (IQR 3–11), 20.5 kg (IQR 13–33), and 118 cm (IQR 94–140), respectively. Of this, 3309 (56.1 %) were diagnosed with CHD; relative frequencies, with number diagnosed by city, altitude, and geographic location within Colombia's regions, are depicted in Fig. 1.

Table 2 shows differences by gender for age, weight and height for the five most frequently encountered CHD. PDA was seen almost twice as frequently in females ($p < 0.0001$), while the opposite was true for Left Ventricular Outflow Tract Obstruction (LVOTO) ($p < 0.0001$). Table 3 shows the five most frequently observed CHD by city of diagnosis. Proportionally, these were ventricular septal defects (VSD) (27.8 %), right ventricular outflow tract obstruction (RVOTO) (16.1 %), auricular septal defects (ASD) (13.8 %), PDA (11.0 %), and LVOTO (9.3 %). There were statistically significant differences by city ($p < 0.0001$) (Fig. 2).

Table 4 shows PDA diagnosis by city (ranked by altitude) and gender. In the five cities at altitudes of 1285 m or more, 14.4 % of all CHD burden was PDA, and 9.3 % in the cities below 500 m ($p < 0.0001$). When compared against all other CHD diagnoses, PDA was associated with increased altitude (ORmh 1.68, 95 % CI 1.34–2.09;

Table 2 Characteristics of patients with the five most frequent congenital heart diseases by gender, 2008–2013

	N	Male				Female			
		n (%)	Age, years P50 (IQR)	Weight, kg P50 (IQR)	Height, cms P50 (IQR)	*n* (%)	Age, years P50 (IQR)	Weight, kg P50 (IQR)	Height, cms P50 (IQR)
VSD	920	456 (49.6)	5.5 (1.6–10)	18 (10–29.5)	108.5 (80.5–134)	464 (50.4)	6 (2–10)	16 (10–26)	105 (80–132)
RVOTO	533	285 (53.5)	7 (3–12)	19.1 (14–32)	115.5 (97.7–140)	248 (46.5)	6 (3–11)	18.5 (12–33.5)	117 (93.2–140.7)
ASD	457	220 (48.1)	5 (2–11)	17.1 (10.1–31.2)	107 (78.5–139)	237 (51.9)	6 (2–11)	17.8(11–28)	105 (84.5–132.5)
PDA	365	133 (36.4)	4 (1–9.2)	15 (9–27)	14 (74.5–133)	232 (63.6)	5 (2–9)	17.5 (11–25.5)	108.5 (84–129.2)
LVOTO	310	206 (66.5)	9 (5–13)	26.5 (16.4–39)	128 (104.7–146.7)	104 (33.5)	9 (4.2–12)	22 (13.9–32.2)	122 (95.2–142.7)

N total with CHD, *n* subjects with CHD by gender, *IQR* interquartile range, *kg* kilograms, *cms* centimeters, *VSD* ventricular septal defect, *RVOTO* right ventricular outflow track obstruction, *ASD* auricular septal defect, *PDA* Patent Ductus Arteriosus, *LVOTO* left ventricular outflow track obstruction

$p < 0.0001$). This association was not modified by gender (OR 1.60 versus 1.81 in females and males, respectively, $p = 0.59$ for homogeneity across gender strata). Similar findings were found with LVOTO and altitude (Table 5); when compared against all other CHD diagnoses, LVOTO was significantly associated with increased altitude (ORmh 2.06, 95 % CI 1.63–2.61; $p < 0.0001$). This association was not modified by gender (OR 1.90 versus 2.15 in females and males, respectively; $p = 0.62$ for homogeneity across gender strata). The opposite was true for the association between RVOTO diagnosis and altitude (OR 0.60; 95 % CI 0.49–0.74, $p < 0.0001$). No association with altitude was found for VSD (OR 0.90; 95 % CI 0.76–1.05, $p = 0.19$) or ASD (OR 1.04; 95 % CI 0.84–1.27, $p = 0.76$).

Discussion

In a large children population with CHD in Colombia, this study found previously unreported associations between LVOTO defects and altitudes as low as 1285 m above sea level, as well as a male gender predominance, and a decrease in the presence of RVOTO defects with altitude. The study also validates and confirms the association of PDA even at moderate altitudes, and its female predominance. The strengths of this study include the systematic and standardized characteristics of the campaigns during six consecutive years in ethnically and geographically diverse regions, the extensive and open nature of the convocations, and the large number of children evaluated and detected with CHD and the reliable diagnostic process with highly specialized medical personnel and echocardiography.

In this study we were not able to document a global predominance of CHD by gender, contrary to what has been described for females at higher altitudes [15, 19]. Similarly, in this study at low and intermediate altitudes, VSD was the most frequently observed CHD, which is in accordance with previous reports in the literature [3, 28].

Decreased oxygen tension at high altitude has been postulated as critical in the observed increase in patency of ductus arteriosus at birth, and hypoxia has been implicated as an extrinsic factor for defective embriogenesis in congenital heart defects [6, 29]. Interventricular defects and atrial septal defects have also been associated with altitude [12–16]. Miao et al. [14] postulated a reasonable pathophysiologic mechanism by which persistently high pulmonary pressures at high altitude after birth could inhibit patent *foramen ovale* closure and predispose to atrial defects. While LVOTO congenital defects (aortic valve stenosis, coarctation of the aorta, and hypoplastic left heart) may have a genetic, heritable component [30], they

Table 3 CHD in patients evaluated during case detection campaigns in 12 Colombian cities, 2008–2013

Cities[a]	CHD (N)	ASD *n* (%)	VSD *n* (%)	PDA *n* (%)	RVOTO *n* (%)	LVOTO *n* (%)	Other CHD *n* (%)
Tunja	104	17 (16.3)	29 (27.8)	14 (13.4)	10 (9.6)	19 (18.2)	15 (14.4)
Duitama	144	39 (27.0)	31 (21.5)	25 (17.3)	10 (6.9)	10 (6.9)	29 (20.1)
Pasto	485	61 (12.5)	160 (32.9)	71 (14.6)	50 (10.3)	54 (11.1)	89 (18.3)
Manizales	348	37 (10.6)	61 (17.5)	45 (13.2)	56 (16.0)	69 (19.8)	80 (22.9)
Ibagué	68	8 (11.7)	22 (32.3)	10 (14.7)	11 (16.1)	5 (7.3)	12 (17.6)
Villavicencio	124	30 (24.1)	34 (27.4)	7 (5.6)	28 (22.5)	9 (7.2)	16 (12.9)
Yopal	108	21 (19.4)	24 (22.2)	11 (10.1)	11 (10.1)	10 (9.2)	31 (28.7)
Cúcuta	309	57 (18.4)	90 (29.1)	41 (13.2)	50 (16.1)	26 (8.4)	45 (14.5)
Valledupar	86	7 (8.1)	25 (29.0)	8 (9.3)	16 (18.6)	7 (8.1)	23 (26.7)
Montería	506	68 (13.4)	174 (34.3)	47 (9.2)	92 (18.1)	21 (4.1)	104 (20.5)
Barranquilla	506	51 (10.0)	145 (28.6)	42 (8.3)	101 (19.9)	32 (6.9)	135 (26.6)
Cartagena	521	61 (11.7)	125 (23.9)	44 (8.4)	98 (18.8)	48 (9.2)	145 (27.8)
	3309	457 (13.8)	920 (27.8)	365 (11.0)	533 (16.1)	310 (9.3)	724 (21.8)

CHD congenital heart disease, *ASD* auricular septal defect, *VSD* ventricular septal defect, *PDA* Patent Ductus Arteriosus, *RVOTO* right ventricular outflow tract obstruction, *LVOTO* left ventricular outflow tract obstruction

[a] Cities appear in order of altitude, from highest to lowest

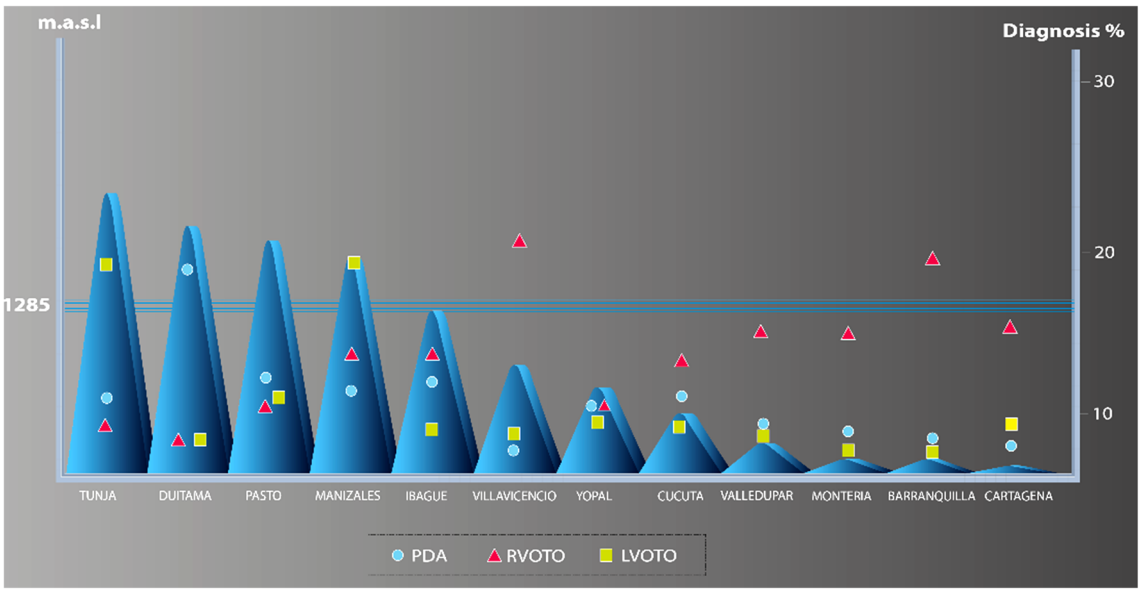

Fig. 2 Patent Ductus Arteriosus (PDA), right ventricular outflow tract obstruction (RVOTO), and left ventricular outflow tract obstruction (LVOTO) according to altitude (m.a.s.l) and frequency (%). In this figure cities are placed in the *x* axis, altitude (meters above sea level, m.a.s.l.) in the main *y* axis and proportion of diagnosis of CHD in the secondary *y* axis (*right*). CHD that showed significant differences when compared by altitude are placed according to these parameters

have not been previously described as associated with altitude. It is interesting to speculate that hypoxia associated with high altitude during pregnancy may increase the frequency of heart defects mentioned above, or that concomitant factors, other than low oxygen tension, but related to high altitude and gender, could be associated with CHD. Populations living at medium and high altitudes exposed to other factors such as climate, temperature, and physical agents (such as mining, industrialization and pollution) may have different socioeconomic, educational, and nutritional status, and the interplay of these different conditions could produce different effects in populations with diverse genetic backgrounds that influence the development of the fetal heart.

Table 4 PDA distribution by gender

Cities[a]	CHD (N)	PDA *n* (%)	Female		Male	
			n (%)	PDA *n* (%)	*n* (%)	PDA *n* (%)
Tunja	104	14 (13.4)	43 (41.3)	6 (13.9)	61 (58.6)	8 (13.1)
Duitama	144	25 (17.3)	73 (50.6)	18 (24.6)	71 (49.3)	7 (9.8)
Pasto	485	71 (14.6)	235 (48.4)	44 (18.7)	250 (51.5)	27 (10.8)
Manizales	348	45 (12.9)	166 (47.7)	27 (16.)	182 (52.2)	18 (9.8)
Ibagué	68	10 (14.7)	34 (50.0)	5 (14.7)	34 (50.0)	5 (14.7)
Villavicencio	124	7 (5.6)	61 (49.1)	5 (8.1)	63 (50.8)	2 (3.1)
Yopal	108	11 (10.1)	61 (56.4)	7 (11.4)	47 (43.5)	4 (8.5)
Cúcuta	309	41 (13.2)	154 (49.8)	22 (14.2)	155 (50.1)	19 (12.2)
Valledupar	86	8 (9.3)	39 (45.3)	4 (10.2)	47 (54.6)	4 (8.5)
Montería	506	47 (9.2)	243 (48.0)	30 (12.3)	263 (51.9)	17 (6.4)
Barranquilla	506	42 (8.3)	250 (49.4)	34 (13.6)	256 (50.5)	8 (3.1)
Cartagena	521	44 (8.4)	274 (52.5)	30 (10.9)	247 (47.4)	14 (5.6)
Total	3309	365 (11.0)	1633 (49.3)	232 (14.2)	1676 (50.6)	133 (7.9)

Patients evaluated during case detection campaigns in 12 Colombian cities, 2008–2013

CHD congenital heart disease, *PDA* Patent Ductus Arteriosus

[a] Cities appear in order of altitude, from highest to lowest

Table 5 Left ventricular outflow tract obstruction distribution by gender

Cities[a]	CHD (N)	LVOTO *n* (%)	Female		Male	
			n (%)	LVOTO *n* (%)	*n* (%)	LVOTO *n* (%)
Tunja	104	19 (18.2)	43 (41.3)	5 (11.6)	61 (58.6)	14 (22.9)
Duitama	144	10 (6.9)	73 (50.6)	3 (4.1)	71 (49.3)	7 (9.8)
Pasto	485	54 (11.1)	235 (48.4)	18 (7.6)	250 (51.5)	36 (14.4)
Manizales	348	69 (19.8)	166 (47.7)	23 (13.8)	182 (52.2)	46 (25.2)
Ibagué	68	5 (7.3)	34 (50.0)	1 (2.9)	34 (50.0)	4 (11.7)
Villavicencio	124	9 (7.2)	61 (49.1)	3 (4.9)	63 (50.8)	6 (9.5)
Yopal	108	10 (9.2)	61 (56.4)	5 (8.1)	47 (43.5)	5 (10.6)
Cúcuta	309	26 (8.4)	154 (49.8)	6 (3.8)	155 (50.1)	20 (12.9)
Valledupar	86	7 (8.1)	39 (45.3)	3 (7.6)	47 (54.6)	4 (8.5)
Montería	506	21 (4.1)	243 (48.0)	8 (3.2)	263 (51.9)	13 (4.9)
Barranquilla	506	32 (6.3)	250 (49.4)	12 (4.8)	256 (50.5)	20 (7.8)
Cartagena	521	48 (9.2)	274 (52.5)	17 (6.2)	247 (47.4)	31 (12.5)
Total	3309	310 (9.3)	1633 (49.3)	104 (6.3)	1676 (50.6)	206 (12.2)

Patients evaluated during case detection campaigns in 12 Colombian cities, 2008–2013

CHD congenital heart disease, *LVOTO* left ventricular outflow tract obstruction

[a] Cities appear in order of altitude, from highest to lowest

The approach followed in this study has weaknesses. Firstly, due to the nature of the campaign itself, this study is not able to provide information on prevalence estimated by city or gender as no random selection of a target population was conducted in any of the regions. Case ascertainment and the catchment population are not complete or easily validated (all children in a given region do not have the same probability of being detected or represented), and almost all children detected during campaigns are, in essence, members of a postnatal dynamic cohort with different detection and survival probabilities in each region (and over time). This should have affected the case mix seen in the campaigns and thus constitute an unrepresentative sample with respect to CHD detected at birth. Due to this, there are limitations that affect postnatal CHD prevalence estimates, and they may be speculative [25, 31]. This limitation, however, should not easily explain the consistent associations found in this study between diagnosis of PDA, LVOTO and RVOTO with altitude and gender, which validate previous findings seen for PDA.

Secondly, in all children we used as surrogate measure for place of birth, the city where CHD diagnosis was made during campaigns; this was necessary given that birth places for many children were small settlements with inaccurate or non-existing altitude estimates. While misclassification of exposure (altitude at birth) for some children is certainly probable due to migration, it is improbable that such misclassification would be differential by city of diagnosis or CHD type: Even if a family of an undiagnosed but symptomatic child would relocate to a lower altitude previous to a campaign, this most likely would have biased results toward the null hypothesis of no association, and an unbiased association estimate could be even larger, especially for LVOTO and PDA.

Confounding by unmeasured genetic predisposition may be possible in our study, but not likely; if altitude is associated with smaller populations, and also likely to have potential cases arriving from more remote locations than at low altitude, reduced genetic diversity predisposing for left ventricular outflow tract obstruction may have been more frequent and may partially help explain our findings. While we believe that this is unlikely at moderate altitudes in Colombia, it is difficult to rule this out, unless a genetic evaluation of the populations screened would have been done. The same can be said of unmeasured environmental exposures in our study. Unfortunately, these measurements were out of the scope of our study.

Finally, differential misclassification of CHD by city of diagnosis (or altitude) is very unlikely and should not explain the observed results; while it is a relatively frequent occurrence that different cardiac defects coexist, cardiac defect classification was done in a standardized fashion irrespective of campaign location.

Conclusions

While the role of genetics or other environmental factors are certainly likely, the results of this study point toward a role for mild-to-moderate altitude above sea level in the occurrence of both PDA and LVOTO in populations with very diverse geographical and ethnical backgrounds, and allow for hypothesis generation on its multifactorial nature.

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Compliance with Ethical Standards

Conflict of interest None of the authors disclose any conflicts of interest.

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