Modeling Geographic Risk of Complex Congenital Heart Defects in Eastern Wisconsin

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Received 8 November 2010; Revised 7 March 2011; Accepted 12 March 2011

BACKGROUND: Geographic variation may be an indicator of risk factors for birth defects. This study models the geographic distribution of three complex congenital heart defects (CHDs) in eastern Wisconsin, and evaluates effects of demographic census variables linked to geographic location. **METHODS:** Cases of Hypoplastic Left Heart Syndrome (HLHS), Tetralogy of Fallot (TOF) and d-Transposition of the Great Arteries (d-TGAs) born between1995 and 2004 were identified from three medical centers serving eastern Wisconsin. Case diagnoses were assigned by a pediatric cardiologist using echocardiographic records. Births by ZIP code were obtained from the State of Wisconsin. ZIP Code demographic variables were derived from 2000 census data. Numbers of cardiac defects by ZIP code were modeled using cluster analysis and Poisson generalized additive models (GAMs) for spatial coordinates including all and white only cases (excluding trisomies). GAM analyses were repeated adjusting for census variables. **RESULTS:** Four hundred forty-eight cases were ascertained. A significant south-to-north spatial gradient for HLHS, TOF, and combined CHDs, but not d-TGAs was identified. This gradient remained significant when census variables were included in the model for the full sample. In the analysis excluding non-white cases, findings were the same for TOF, combined CHDs, and d-TGAs. However, the geographic gradient for HLHS was not significant in the adjusted model. **CONCLUSIONS:** A south-to-north gradient was apparent for two of three complex CHDs in eastern Wisconsin. For white cases, demographic variation seems to explain some of this spatial gradient in HLHS. Further studies are needed to confirm demographic and other risk factors underlying this geographic gradient. *Birth Defects Research (Part A) 91:631–641, 2011.* © 2011 Wiley-Liss, Inc.

Key words: congenital heart disease; disease mapping; ZIP code; census data; socioeconomic factors

INTRODUCTION

In spite of the significant impact of congenital heart defects (CHDs) on child morbidity and mortality, understanding of etiologic factors of this class of birth defects is limited. About 18 to 20% of CHD cases are associated with chromosomal disorders or single gene disorders and syndromes where underlying genes have been discovered (Pierpont et al., 2007). An additional 5% or less are due to known maternal non-inherited causes or gene/environment interactions including exposure to teratogenic drugs, folate status, febrile illness during early pregnancy, diabetes, obesity, and a range of life style factors (Allen et al., 2001; Hobbs et al., 2005; Hobbs et al., 2010; Mills et al., 2010). Environmental exposures are thought to interact with genetic endowment for many types of congenital heart defects (CHDs; Botto and Goldmuntz, 2008). However, reliably documenting effects of environmental exposures has been challenging. The Baltimore Washington

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This work was supported by the Children's Research Institute, Children's Hospital of Wisconsin and National Institutes of Environmental Health Sciences (NIEHS) grant P30ES004184-23.
Some material included in this article was presented at the 13th annual meeting of the National Birth Defects Prevention Network, March 8–9, 2010, National Harbor, Maryland.
Published online 31 May 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/bdra.20828

Table 1
Diagnostic Codes used to Identify Cases of d-TGA, HLHS, and TOF

	Children's Hospital of Wisconsin Marshfield Clinic and St. Vincent Medical Records (ICD-9 Codes)	Herma Heart Center and Wisconsin Pediatric Cardiac Registry
d-TGA-related	745.1-d-TGA 745.11-DORV 745.12-L-TGA	234-d-TGA 235-DORV 237-L-TGA 383-Rastelli (d-TGA repair) 830-L-TGA repair
HLHS-related	746.7-HLHS 746.3-Aortic stenosis 746.84-Shones	136-HLHS 325-Shones 333-Norwood
TOF-related	745.2-TOF 746.01-Pulmonary valve atresia	240-TOF 385-TOF repair 804-AVSD/TOF repair

d-TGA, d-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; ICD, International Classification of Diseases; DORV, double outlet right ventricle; L-TGA, levo-transposition of the great arteries; AVSD, atrioventricular septal defect.

Infant Study (Ferencz et al., 1985; Brenner et al., 1989; Beaty et al., 1991; Correa–Villaseñor et al., 1993; Ferencz et al., 1997; Loffredo et al., 2001; Kuehl and Loffredo, 2002; Hwang and Jaakkola, 2003; Kuehl and Loffredo, 2006), other smaller studies (Yauck et al., 2004; Brender et al., 2008; Chi et al., 2008; Langlois et al., 2009) and the National Birth Defect Prevention Study (Rasmussen et al., 2002) have reported exposures associated with CHDs, or demonstrated geographic clustering of cases likely related to localized environmental exposures.

Prompted by clinical observation of an unusually large number of Hypoplastic Left Heart Syndrome (HLHS) cases treated at Children's Hospital of Wisconsin (CHW), we documented an elevated prevalence as well as an indication of geographic clustering of this CHD in eastern Wisconsin (Cronk et al., 2004). The present study expands on the 2004 analysis with a focus on evaluating the geographic distribution of cases of three complex CHDs, as well as completing preliminary analyses of demographic factors potentially related to geographic case distribution.

MATERIALS AND METHODS

This study was reviewed and approved by the CHW Institutional Review Board. Three complex heart defects, HLHS, Tetralogy of Fallot (TOF), and d-transposition of the great arteries (d-TGAs) were selected for evaluation. Each of these defects requires intervention (usually surgery) within the first weeks of life at the medical centers where the study was conducted. Thus, we had the potential for reasonably complete ascertainment. Because all of these CHDs are relatively low prevalence, cases born over a 10-year period (between 1995 and 2004) were included.

Case Finding

Case ascertainment used the following sources: (1) CHW medical records; (2) the Herma Heart Center Cardiac database (the clinical database maintained within the Division of Pediatric Cardiology and Cardiothoracic Surgery at CHW); (3) the Wisconsin Pediatric Cardiology Registry, a research database initiated and housed at CHW since 2000 in which patients with CHD are voluntarily enrolled from multiple facilities throughout Wisconsin (Hanson–Morris and Pelech, 2006; Person et al., 2006); (4) medical records from the Marshfield Clinic in Marshfield, Wisconsin (a large multidisciplinary group practice with an active research program serving northern, central and western Wisconsin); and (5) medical records at St. Vincent's Hospital, Green Bay, Wisconsin, the largest medical center treating CHDs in east central Wisconsin. Queries included codes for the three target lesions and for diagnoses closely related to these conditions (Table 1). The Wisconsin Birth Defects Registry (WBDR) could not be used as a source of case numbers because the WBDR only began collecting reports in 2004 (the end of the period analyzed). Moreover, cases of CHD for 2007 registered in the Wisconsin Pediatric Cardiology Registry (one of the sources used in the present study) were nearly two times greater than those reported to the WBDR (Wisconsin Bureau of Community Health Promotion, 2007) in the same year, indicating significantly incomplete case ascertainment.

To identify cases missed because of death before diagnosis or treatment, we obtained data from the Wisconsin Bureau of Health Information and Policy (WBHIP) for infant deaths with birth dates between 1995 and 2004 and International Classification of Diseases (ICD)-9 or ICD-10 codes for the target diagnoses either as the underlying cause of death or any other automated classification of medical entities codes listed on the death records. We used probabilistic matching based on diagnosis, ZIP code, and birth year to identify unique cases not identified from other sources used in case finding. We could not use the ascertainment methods described below (i.e., by assigning the diagnosis based on the pediatric cardiologist's evaluation of the echocardiogram results) on cases only identified in the death files. Consequently, these cases were used to assess the completeness of our ascertainment, but were not included in the computation of prevalence rates or in the geographic analyses. We did not ascertain cases of these three defects among stillborns (fetal deaths), miscarriages, or terminations.

Case Ascertainment and Confirmation

Information on diagnosis, surgical procedures, accompanying conditions, demographics, and a limited number

of additional risk factors was abstracted by a single researcher (S. Cossette). Diagnostic information (including patient echocardiogram) was evaluated in consultation with the pediatric cardiologist, and cases without evidence of one of the three conditions were excluded.

Inclusions

Inclusion criteria for cases were as follows:

- Birth residence within one of the target ZIP codes in 44 counties in eastern Wisconsin. To increase the probability of complete ascertainment, we excluded cases from the western counties, where some cases may have been missed because they received care at out-of-state facilities (e.g., in Minneapolis or Rochester, Minnesota).
- Confirmation of birth address based on: (1) a date of hospital admission within 2 months of birth with the address at the time of admission recorded in the medical record; or (2) a report in the medical record dated within 2 months of birth that included address information.
- Diagnosis confirmed by review of the echocardiogram: echocardiograms were reviewed by the pediatric cardiologist and assigned a diagnostic code using the case criteria specified below. These codes were used in the remainder of the analysis.

Exclusions

Any child who was 'adopted' (based on statements in the medical record) was excluded.

Case Definition

A pediatric cardiologist (A. N. Pelech) reviewed and assigned diagnoses for all cases based on the evidence available from postnatal echocardiogram reports in that patient's file. Identifiers were redacted from all files. For each case, a primary and, if appropriate, joint primary and/or secondary diagnoses were specified. Diagnostic assignment used the following criteria:

(a) Cases assigned the d-TGA diagnosis exhibited an aorta arising from a morphologic right ventricle and a pulmonary artery arising from a morphologic left ventricle (atrioventricular concordance and ventriculoarterial discordance). Great arterial spatial relationships did not enter into case classification. Cases with ventricular septal defects (VSDs) were included as long as the criterion for double outlet right ventricle (DORV; i.e., >50% aortic override and bilateral conus) was not met. Levo-transposition of the great arteries and DORV cases were not included.

(b) HLHS included a spectrum of cardiac abnormalities characterized by marked hypoplasia of the left ventricle, left heart structures, and ascending aorta. The aortic and mitral valves were either atretic, hypoplastic, or stenotic. A patent ductus arteriosus was invariably present. Features present in some cases included VSDs of the interventricular septum, atrial septal defects, and aortic coarctation. Notably, individuals with unbalanced atrioventricular septal defects with left heart hypoplasia were excluded. By definition, the left heart was unable to independently sustain adequate systemic cardiac output (Noonan and Nadas, 1958).

(c) Cases of TOF included: (1) a large unrestrictive malalignment perimembranous VSD; (2) overriding of the aorta over the septal defect; (3) right ventricular outflow obstruction; and/or (4) right ventricular hypertrophy. Cases also included the severe variant form with atresia of the outflow tract, so-called TOF with pulmonary atresia. Cases of DORV with subaortic VSD and pulmonary stenosis were excluded (Baker and Anderson, 2010).

Birth Data

The number of births occurring between 1995 and 2004 by ZIP code was obtained through a data sharing agreement with the WBHIP.

ZIP Code Level Census Data

We used the method pioneered by Krieger (1992) to preliminarily evaluate socioeconomic/demographic factors potentially underlying geographic variation. Census 2000 ZIP code-specific demographic variables were downloaded from the American Fact Finder website (US Census Bureau, 2011) and linked to the ZIP code aggregated CHD and geographic coordinate data.

Statistical Analysis

Overall birth prevalence rates for the three target diagnoses were computed using summed cases and births across all included ZIP codes. Birth or case addresses that listed post office box ZIP codes were assigned to the enclosing residential ZIP code specified in the ZIP code database (Geographic Data Technology, 2011). Births or cases that listed non-residential unique ZIP codes (usually associated with a building or organization) were assigned to the nearest residential ZIP code. Geographic centroids for ZIP codes were used in the geographic analyses.

For the geographic analyses, we used two methods: (1) the spatial scan statistic to detect local excess numbers of cases, or geographic clustering (Kulldorff and Nagarwalla, 1995);and (2) a generalized additive model (GAM) to explore continuous changes in risk across the study region (Hastie and Tibshirani, 1990; Wood, 2006). For the first analysis, we applied the Poisson model-based spatial scan statistic using SatScan™ (Martin Kulldorff & Information Management Services, Boston MA) software (v.8.0) to test the null hypothesis of constant CHD rate (per birth) across the study region against the alternative of an elevated CHD rate (per birth) inside at least one circular scanning window. The maximum scanning window was set to include 50% of the total population. The p values were calculated using 9999 Monte Carlo simulations under the null hypothesis. Separate analyses were run for each CHD and the three CHDs combined. For the second analysis, numbers of CHDs by ZIP code were modeled using a Poisson generalized additive regression model (GAM) with a log link function. GAM is used when non-linear relationships are anticipated between dependent and predictor variables. For each ZIP code, (log) number of live births was included in the model as an offset term to account for variable number of births at risk. The location of the ZIP code centroid – south-to-north and west-to-east in the Wisconsin Universal Transverse Mercator (WUTM) coordinate system which directly reflects latitude and longitude – was included in the model as a penalized two-dimensional thin plate regression spline with smoothing parameter chosen by generalized cross-validation (Wood, 2003; Wood, 2006;

Table 2
Birth Prevalence per 10,000 for the Full Sample and for Whites (Excluding Cases with Trisomies)

Diagnosis	ICD-9 Codes	N	Prevalence (per 10,000)	Poisson 95% CI
Hypoplastic left heart syndrome	746.7			
All cases[a]		127	2.25	1.88, 2.68
Whites only (excluding trisomies)[b]		104	2.39	1.96, 2.90
d-transposition of the great arteries	745.1			
All cases[a]		126	2.24	1.86, 2.66
Whites only (excluding trisomies)[b]		97	2.23	1.81, 2.72
Tetralogy of Fallot	745.2			
All cases[a]		195	3.46	2.99, 3.98
Whites only (excluding trisomies)[b]		132	3.04	2.54, 3.60
Combined defects	746.7, 745.1, 745.2			
All cases[a]		448	7.95	7.23, 8.72
Whites only (excluding trisomies)[b]		333	7.66	6.86, 8.53

[a]Total births for included ZIP codes was 563,478.
[b]Total Non-Hispanic white births for included ZIP codes was 434,586. ICD, International Classification of Diseases; CI, confidence interval.

Wood, 2008). The term 'thin plate' draws an analogy to the bending of a thin sheet of metal laid on an irregular surface. Thin plate splines are used to fit arbitrarily spaced (in this case, ZIP code centroids) count data. The larger the case counts the bigger the deflection of the thin plate. To arrive at the final model, potential simplifications of the ZIP code location effect as additive functions of north-to-south and east-to-west were evaluated based on Akaike's Information Criterion (Akaike, 1974). This allowed us to evaluate a wider range of spatial variation, including spatial trends in non-cardinal directions (e.g., southwest-to-northeast rather than south-to-north) and more complex, non-linear spatial patterns. This approach provides protection from the implicit multiple testing problem based on the essentially arbitrary choice of cardinal directions in the parametric model.

We assessed four models for each CHD and the three CHDs combined. Using all cases, we evaluated models for the spatial effects (unadjusted model). This model was then adjusted for ZIP code level US Census variables (adjusted model) possibly underlying geographic variation. The adjusted model included the following variables: percent rural, percent white, median age of women, median home value, median family income, percent unmarried head of household, percent of households with college degree, percent of households with less than high school education, percent employed, and the percent of families with children living below the poverty line. Detailed definitions for all included US Census variables can be accessed at www.census.gov (US Census Bureau, 2001). Because non-white populations are concentrated in the southern portion of eastern Wisconsin, we fit the unadjusted and adjusted models excluding all non-white patients with CHD. Numbers of non-white cases were too small to allow separate analyses to be completed. Because trisomies may represent cases with differing etiologies, we also excluded all cases with trisomies from this latter analysis. The same set of census variables were used in the adjusted model for the analysis including only white cases (and excluding trisomies) with the exception of percent of the white population. All analyses were performed using R (R Development Core Team, 2010).

RESULTS

Births in Target Geographic Area

There were 563,478 total and 434,586 non-Hispanic white births in the geographic area of study representing about 80% of total Wisconsin births during this period (1995–2004).

Case Identification

A total of 968 potential cases were identified. Based on evaluation of echocardiogram results the pediatric cardiologist confirmed 567 (58.6%) cases of HLHS, d-TGA, and TOF. The most common diagnoses assigned to excluded cases were aortic stenosis (n = 91), atrioventricular septal defect (n = 51), DORV (n = 61), Shone's syndrome (n = 17), and levo-transposition of the great arteries (n = 12). Of the 83 infant deaths identified in the Wisconsin death files, 56 were matched to one of the potential cases and 27 were not matched. Of the 27 cases uniquely identified in the infant death files, 22 were coded as HLHS (10 from southeast ZIP codes,7 from south central ZIP codes, and 5 from northeast ZIP codes), 2 as d-TGA, and 3 as TOF. These cases were not included in the prevalence estimates because their diagnoses could not be confirmed by the methodology used for all other cases.

Of the 567 eligible cases, birth addresses for 32 (5.6%) could not be verified, 73 (13%) lived outside the target area, 8 (1.4%) were noted as 'adopted' in the medical record, and 6 (1%) were excluded for other reasons (e.g., mismatch of identifying information among sources). Table 2 lists numbers, birth prevalence rates and 95% Poisson confidence intervals (CIs) for all target diagnoses for the full sample and for the sample including only whites (and excluding trisomies). Birth prevalence was around 2 per 10,000 for HLHS and d-TGA, and about 3.5 per 10,000 births for TOF in the full sample. Birth prevalences for the white sample were not significantly different from those for the full sample. Poisson regression analysis showed no significant annual temporal variations. However, the largest numbers of cases were observed in 1996, 1998, and 1999.

Table 3
Distribution of Census Demographic Variables for 486 ZIP Codes used in the Adjusted Models and Pearson Correlation Coefficients (±95% CI) with WUTM coordinates

Census variables used in adjusted model			WUTM west-to-east[a]			WUTM south-to-north[a]		
	Mean	SD	R	95% CI		R	95% CI	
Percent rural	63.0	41.4	**−0.36**	**−0.44**	**−0.28**	**0.42**	**0.34**	**0.49**
Percent white population	94.6	13.0	**−0.21**	**−0.29**	**−0.12**	**0.12**	**0.03**	**0.20**
Female age (median) (years)	38.6	4.9	−0.06	−0.15	0.03	**0.41**	**0.33**	**0.48**
Home value (median)	$112,021	$36,164	**0.28**	**0.19**	**0.36**	**−0.30**	**−0.38**	**−0.22**
Family income (median)	$55,523	$11,915	**0.28**	**0.19**	**0.36**	**−0.38**	**−0.46**	**−0.30**
Percent unmarried head of household	5.0	1.8	**−0.09**	**−0.18**	**0.00**	**−0.10**	**−0.19**	**−0.01**
Percent college degree (population ≥25 years)	18.4	11.0	**0.18**	**0.09**	**0.26**	**−0.28**	**−0.36**	**−0.19**
Percent less than high school education (population ≥25 years)	15.4	6.5	−0.06	−0.15	0.03	**0.18**	**0.10**	**0.27**
Percent employed (≥16 years, ≥40 weeks in 1999)	69.0	8.3	0.01	−0.08	0.10	**−0.40**	**−0.47**	**−0.32**
Percent families with children <18 years below the poverty line	8.9	8.7	−0.01	−0.09	0.08	0.08	−0.01	0.17

[a]Bolded values are statistically significant. CI, confidence interval; WUTM, Wisconsin Universal Transverse Mercator.

Demographic and Other Person Factors of Cases

Among ascertained cases, 48 were reported as deceased in the medical records, and an additional 12 cases were probabilistically matched to the WBHIP infant death records. Seventy percent of total deceased cases had ICD-9 or ICD-10 codes for HLHS (n = 34), 6 were coded as d-TGA, and 8 were coded as TOF. The preponderance of cases were boys (about 62%), with d-TGA cases significantly more likely to be boys (72% vs. about 56% for each of the other diagnoses; chi-square = 10.24; $p < 0.01$). Eighty percent (n = 347) of all cases were white, 10% were African American/black, and the remaining 10% were Hispanic (white or non-white), or other (American Indian, Hmong, Asian, and Other). Average age for case mothers was about 29 years (SD 5.8; range, 15.8–43.4 years). HLHS and TOF cases were more likely than d-TGA cases to be delivered before 37 weeks of gestation (chi-square = 11.7; $p < 0.01$). About 14% of mothers reported substance use (cigarettes, alcohol, cocaine, or other illicit drugs); 9% reported use of antidepressants. Mothers of HLHS and d-TGA were more likely to have used antidepressants than mothers of infants born with TOF. A family history of birth defects (including CHDs) was documented for about 12% of cases, with no differences apparent across diagnoses. Four percent of cases (n = 18) were noted to have Trisomy 21 or some other Trisomy, and most of these were TOF cases. About 4% of case mothers had any type of diabetes (gestational, type I or type II). About 26% of mothers were obese (body mass index >30).

ZIP Codes and Census Demographic Variables

A total of 611 ZIP codes (486 residential ZIP codes, and 125 unique or post office box ZIP codes recoded to one of the residential ZIP codes) were included in the analysis. Table 3 presents distributions for the selected census variables used in the adjusted models and their correlations with WUTM (longitude and latitude) coordinates for the 486 ZIP codes included in the analysis. With the exception of median percent rural and median family income, values for other census variables for included ZIP codes did not differ from the state of Wisconsin. Median family income ($55,523) was slightly higher than the Wisconsin median ($52,911). Because the average of median percent rural was computed with all ZIP codes having equal weight (i.e., without respect to the size of the population in that ZIP code), it is not strictly comparable to figures for the state of Wisconsin. However, the percent of the total population living in rural areas in these ZIP codes (about 25%) was slightly lower than that for the state of Wisconsin as a whole (about 31%).

Some bivariate correlations between the census variables and the WUTM west-to-east and south-to-north coordinates were statistically significant although none was >0.5. Correlations between about 0.3 and 0.4 with WUTM for south-to-north coordinates were apparent for percent rural, median age of women, median family income and percent employed (the further north, the greater rurality and higher median age of women; the further north, the lower the median income, median home value, and the percent employed).

Geographic Analysis

The spatial scan statistic identified a single significant cluster of elevated risk for all three CHDs combined (relative risk, 1.78; 111 cases; 70 expected cases; $p = 0.0017$). The cluster consisted of 107 ZIP codes covering almost the entire northern portion of the study region. Similar large clusters encompassing the bulk of the northern portion of the study region were seen for HLHS (134 ZIP codes; relative risk, 2.24; 42 cases; 23 expected cases; $p = 0.066$) and for TOF (142 ZIP codes; relative risk, 1.85; 52 cases; 32 expected cases; $p = 0.25$), but not for d-TGA (3 ZIP codes near Sheboygan; relative risk, 6.45; 5 cases; 0.8 expected cases; $p = 0.63$).

Table 4 gives the results for both the unadjusted and adjusted GAM models for the full sample and whites only (excluding trisomies). Figures 1-4 show maps of the estimated rates by ZIP code for each CHD and the three CHDs combined for the unadjusted model for the full sample. For this model, there was significant spatial variation in risk for HLHS ($p = 0.005$), for TOF ($p = 0.03$), and for the three cardiac defects combined ($p = 0.0004$), but not d-TGA ($p = 0.60$). Parametric models for south-to-north, and west-to-east provided the same fit as the

Table 4
Estimated relative risks (RRs) (+95% CIs) for 100 km Change from West-to-East (Easting) or South-to-North (Northing) from Poisson Generalized Linear Models for the Full Sample, Whites only (Excluding Trisomies) Unadjusted and Adjusted for Census Demographic Variables

Full sample

	Unadjusted				Adjusted[a]			
	RR	95% CI		*p* value	RR	95% CI		*p* value
Combined defects								
Easting (per 100 km)	1.05	0.88	1.25	0.57	1.12	0.90	1.38	0.311
Northing (per 100 km)	**1.25**	**1.12**	**1.39**	**0.00008**	**1.25**	**1.09**	**1.44**	**0.002**
Hypoplastic Left Heart Syndrome								
	RR	95% CI		*p* value	RR	95% CI		*p* value
Easting (per 100 km)	1.12	0.80	1.55	0.51	1.25	0.83	1.90	0.29
Northing (per 100 km)	**1.40**	**1.14**	**1.71**	**0.0011**	**1.38**	**1.04**	**1.82**	**0.026**
Tetralogy of Fallot								
	RR	95% CI		*p* value	RR	95% CI		*p* value
Easting (per 100 km)	1.07	0.82	1.39	0.62	1.14	0.82	1.57	0.44
Northing (per 100 km)	**1.25**	**1.06**	**1.48**	**0.0085**	**1.34**	**1.09**	**1.65**	**0.006**
D-Transposition of the Great Arteries								
	RR	95% CI		*p* value	RR	95% CI		*p* value
Easting (per 100 km)	0.97	0.70	1.34	0.84	0.98	0.66	1.46	0.94
Northing (per 100 km)	1.10	0.89	1.36	0.36	1.00	0.77	1.29	0.98

Whites Only, Excluding Trisomies Combined Congenital Heart Defects

	Unadjusted				Adjusted[b]			
	RR	95% CI		*p* value	RR	95% CI		*p* value
Combined defects								
Easting (per 100 km)	0.93	0.77	1.13	0.482	1.02	0.80	1.30	0.853
Northing (per 100 km)	**1.36**	**1.20**	**1.54**	**0.0000007**	**1.27**	**1.09**	**1.49**	**0.002**
Hypoplastic Left Heart Syndrome								
	RR	95% CI		*p* value	RR	95% CI		*p* value
Easting (per 100 km)	1.08	0.75	1.54	0.68	1.24	0.80	1.93	0.33
Northing (per 100 km)	**1.42**	**1.14**	**1.77**	**0.0017**	1.28	0.97	1.68	0.077
Tetralogy of Fallot								
	RR	95% CI		*p* value	RR	95% CI		*p* value
Easting (per 100 km)	0.91	0.67	1.22	0.52	1.01	0.71	1.45	0.95
Northing (per 100 km)	**1.45**	**1.21**	**1.75**	**0.00009**	**1.55**	**1.22**	**1.96**	**0.0003**
D-Transposition of the Great Arteries								
	RR	95% CI		*p* value	RR	95% CI		*p* value
Easting (per 100 km)	0.84	0.58	1.20	0.33	0.90	0.58	1.38	0.62
Northing (per 100 km)	1.17	0.93	1.48	0.18	0.91	0.68	1.21	0.50

[a]Adjusted for percentage of rural, percentage of white, median age of women, median home value, median family income, percentage of unmarried head of household, percentage with college degree, percentage with less than high school education, percentage of employed, and percentage of families below the poverty line.
[b]Adjusted for percentage of rural, median age of women, median home value, median family income, percentage of unmarried head of household, percentage with college degree, percentage with less than high school education, percentage of employed, and percentage of families below the poverty line. CI, confidence interval; RR, rate ratios;

full generalized additive models for all outcomes. Estimated risk ratios from the parametric model were significant for south-to-north risk gradients for HLHS (risk ratio per 100 km north 1.40; 95% CI, 1.14–1.71; $p = 0.0011$), for TOF (risk ratio per 100 km north 1.25; 95% CI, 1.06–1.48; $p = 0.0085$) and for all defects combined (risk ratio per 100 km north 1.25; 95% CI, 1.12–1.39; $p = 0.000008$), but not for d-TGA (risk ratio per 100 km north 1.10; 95% CI, 0.89–1.36; $p = 0.36$). There was no significant west-to-east gradient for any outcome (HLHS: $p = 0.51$; TOF: $p = 0.62$; TGA: $p = 0.84$; all defects: $p = 0.57$). Adjustment for ZIP code level census variables did not alter these findings for the full sample.

For the analysis including only White cases (and excluding trisomies), relative risks for the unadjusted model were not different from those for the analysis including all cases. In the model adjusting for census variables, the significance of the south-to-north effect did not change for TOF or the combined defects. For HLHS, the south-to-north effect was not statistically significant at $p < 0.05$, although the relative risk for HLHS in this model (1.28) fell within the confidence limits for the unadjusted model (1.14–1.77). Two census variables were significant in this model, median age of women (increasing risk with higher age) and median home value (decreasing risk with increasing home value).

DISCUSSION

This study documents a south-to-north gradient for two CHDs (HLHS and TOF) and for the combined three types of CHD cases in eastern Wisconsin over a 10-year period.

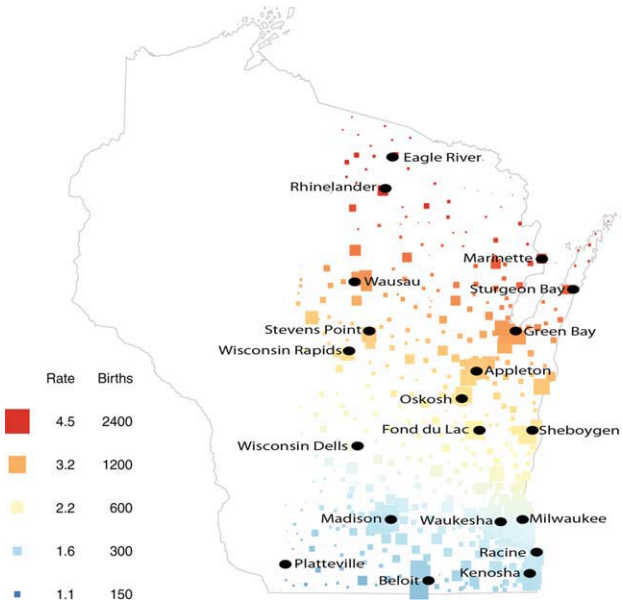

Figure 1. Estimated rates by ZIP code for hypoplastic left heart syndrome (HLHS) for the generalized additive model (GAM) unadjusted model for the full sample.

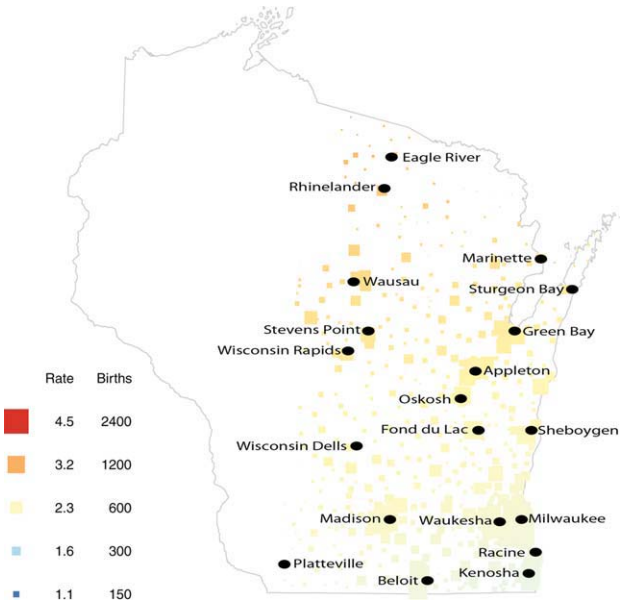

Figure 3. Estimated rates by ZIP code for d-Transposition of the Great Arteries (d-TGA) for the generalized additive model (GAM) unadjusted model for the full sample.

Other analyses indirectly supported these findings, including identification of weak clusters of HLHS in specific northeastern counties, and simple correlation of CHD prevalence and latitude centroids for ZIP codes (data not shown). The relationship of ZIP code level census variables to geographic case distribution was also evaluated. While some of these variables had significant simple correlations with south-to-north coordinates, in most cases, adjustment of the GAM regression models for the census variables did not alter the strength of the south-to-north geographic gradient. For HLHS among white cases (and excluding trisomies), the strength of the south-to-north gradient was diminished in the adjusted model. Two census variables (increasing median female age and decreasing home value) may partially explain the observed south-to-north increase in white HLHS cases.

South-to-north gradients have been identified for a number of diseases or health indicators including multi-

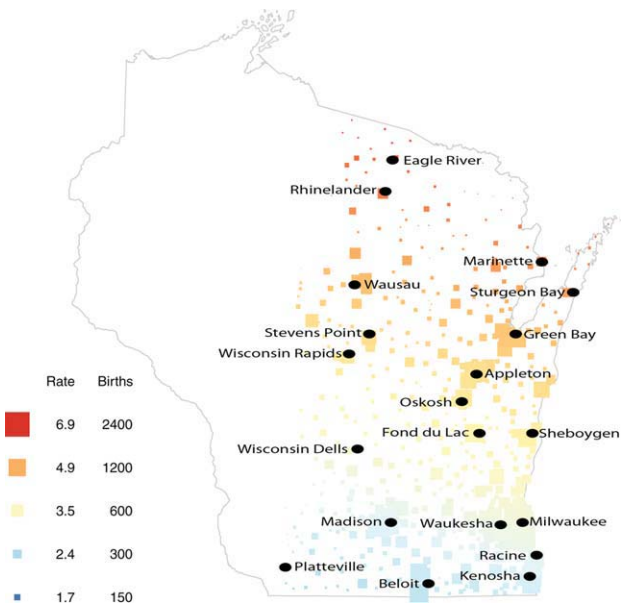

Figure 2. Estimated rates by ZIP code for tetralogy of Fallot (TOF) for the generalized additive model (GAM) unadjusted model for the full sample.

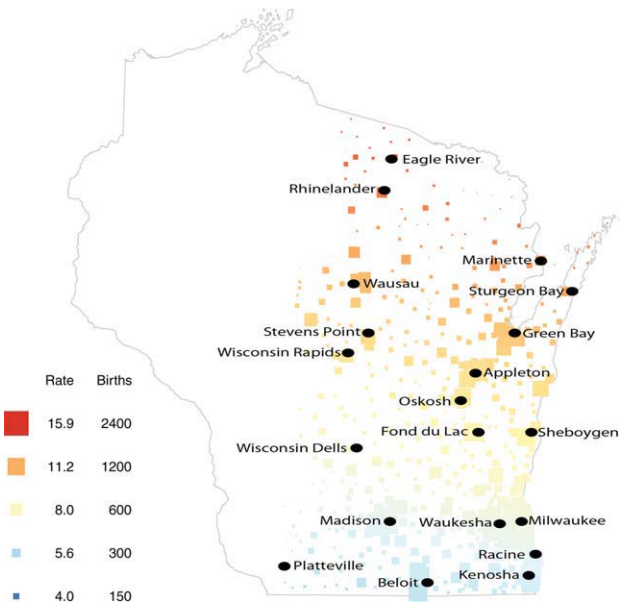

Figure 4. Estimated rates by ZIP code for the three congenital heart defects (CHDs) combined for the generalized additive model (GAM) unadjusted model for the full sample.

ple sclerosis (MS; Hogancamp et al., 1997; Fromont et al., 2010), inflammatory bowel disease (Nerich et al., 2006; Nerich et al., 2010), cardiovascular disease and stroke (Cottel et al., 2000; Morris et al., 2001; Morris et al., 2003), and perinatal mortality (Tromp et al., 2009). However, the assumption is that geographic gradients are underlaid by linked gradients with more plausible association with CHD occurrence. Some of these studies have deconstructed the geographic/place association into specific risk factors occurring in a south-to-north gradient. Nerich et al. (2010) found urbanicity and poor sanitary house equipment (related to location) to be associated with an increased risk of Crohn's disease, although northern latitude had an additional independent effect. Co-occurrence of multiple cardiovascular disease risks partially accounted for the increasing south-to-north/east distribution of cardiovascular disease in France (Cottel et al., 2000; Morris et al., 2003). Noonan et al. (2010) evaluated three cohorts for patterns of MS occurrence in the United States, and concluded that UV exposure was highly associated with disease occurrence. Two studies, one of inflammatory bowel disease and the other of MS, identified geographic gradients (clines) related to ancestry/genetics (Hogancamp et al., 1997; Price et al., 2008).

Our analysis indicated weak but significant associations of some demographic variables to geographic location (Table 3), although few of these appeared to override the south-to-north gradient effect. Yang et al. (2008) found weak associations between socioeconomic status (SES) and occurrence of TOF and d-TGA. Households with the lowest SES using combined indicators were at greatest risk for d-TGA, but not TOF. Carmichael and Shaw (2000) found higher rates of conotruncal defects among women with less than a high school education experiencing stressful events periconceptionally or during early pregnancy. SES gradients may also be related to quality of health care. Meyer and Siega–Riz (2002) found that declines in birth prevalence of spina bifida after the addition of folic acid to enriched grain products were greater in white women and better educated women over age 30 years with private insurance. Folic acid supplementation has been shown to be related to decreases in CHDs (Shaw et al., 1995; Botto et al., 2000; Bailey and Berry, 2005; Ionescu–Ittu et al., 2009; van Beynum et al., 2010). We observed an effect of median house value, one measure of SES, on HLHS cases that was also associated with geographic location. Direct measures of the risk/protective factors underlying this SES gradient would likely improve the explanation of CHD risks.

We were not able to evaluate specific environmental exposures associated with geographic location. The initial clinical perception of elevated rates of HLHS was anecdotally associated with the Lower Fox River in Northeast Wisconsin where significant polychlorinated biphenyl contamination (PCB) of land and drinking water from the highest concentration of pulp and paper mills in the world is documented (Renner, 2001; Cacela et al., 2002; Imamoglu et al., 2004). PCB exposure has been associated with birth defect occurrence in animal models (Marks et al., 1989; Hatano and Hatano, 1994; Pocar et al., 2005; Kopf and Walker, 2009). Epidemiologic studies, however, have been inconsistent in documenting associations with birth defects in humans and PCB exposure (Croen et al., 1997; Orr et al., 2002; Suarez et al., 2005; Wigle et al., 2008).

Several studies have observed an association of birth defects or CHDs specifically with maternal residence in rural/agricultural areas (Dorsch et al., 1984; Garry et al., 1996; Cedergren et al., 2002; Garry et al., 2002; Schreinemachers, 2003; Chi et al., 2008; Winchester et al., 2009). Langlois et al. (2010) demonstrated that TOF was most prevalent in rural areas particularly those with the greatest percentage of land in crops. The measure of rurality available from the Census 2000 data (percent of population living in areas classified as rural) was correlated with the south-to-north coordinate (0.42, Table 3), but did not significantly contribute to explaining the risk for any CHD. The Census Bureau's classification of ''rural'' consists of all territory, population, and housing units located outside of urban areas or urban clusters, including non-agricultural areas. Substitution of a variable such as percentage of land in crops more directly linked to agricultural chemical exposures associated with CHD occurrence would likely improve the explanatory power of this variable. A 2007 survey of agricultural chemicals in Wisconsin groundwater showed pesticide contamination in 33.5% of rural drinking water wells with the frequency of contamination greater in areas of the state with higher intensity of agriculture (Wisconsin Department of Agriculture, 2008). Another Wisconsin study quantifying agriculture chemical concentrations in streams, which replenish the water tables from which drinking water is extracted, found low concentrations in all streams sampled independent of the pesticide application season or the hydrologic stage of the river (Wisconsin Department of Agriculture, 2009). This finding further supports agricultural chemical contamination of drinking water in rural areas.

The rates we observed for two of the three defects (HLHS and TOF) were similar to those reported for active US surveillance systems for the period 1999 to 2001 (Canfield et al., 2006a; Centers for Disease Control and Prevention (CDC), 2006; Parker et al. 2010) and in meta-analyses (Hoffman and Kaplan, 2002). The most recent estimate for d-TGA from the National Birth Defects Prevention Network (NBDPN) data for active registries is higher than observed in this study (3 per 10,000 vs. 2.2 per 10,000 respectively). For d-TGA, we excluded codes 745.11 through 745.19 (DORV, L-transposition, and other transposition of the great vessels) which are included in the NBDPN case definitions. This may partially account for some of the discrepancy. In general, the fact that our rates are similar to NBDPN rates supports the completeness of our case ascertainment.

Birth prevalence estimates for the three defects reported in this article differ from those originally presented in the 2004 article (Cronk et al., 2004). This difference is likely due to differing methods used in the two studies. For the 2004 article, diagnoses were determined from medical record review and echocardiograms evaluated by a pediatric cardiologist only if discrepant codes were found. For the present study, a pediatric cardiologist reviewed all of the echocardiograms and assigned a diagnosis to each case. In addition, specific criteria were required for determination of birth address whereas in 2004, the first address provided in the medical record was used. Finally, in the present study, assignment to the target area was completed using a more specific ZIP code criterion. It is notable that running averages for prevalence of HLHS peaked in 1999 (at 2.75 per 10,000

births) and have declined since that time to 1.58 (for the years 2002–2004). Using the methods from the 2004 article, (using diagnosis from the identification source and assuming the recorded address was the address at birth), case numbers would have been substantially greater than those reported for the present study (n = 160 for HLHS; 148 for d-TGA; and 224 for TOF).

Our study had several important strengths. We limited case finding to geographic areas where relatively complete case ascertainment could be achieved, and used multiple sources to enhance the probability of complete ascertainment. All diagnoses were assigned by a single pediatric cardiologist using echocardiographic records. Variation in diagnostic assignment should therefore have been limited, and would not bias the south-to-north geographic pattern documented in our analysis. Data were analyzed at the finest available spatial resolution, which should minimize the impacts of the modifiable areal unit problem (i.e., the imposition of artificial spatial units on a continuous geographical phenomenon; Openshaw and Taylor, 1979). Birth prevalence rates were computed using summed births across all included ZIP codes (n = 563,478). In an earlier study (Cronk et al., 2004), areas with a higher prevalence of HLHS were identified by aggregating eastern Wisconsin counties into five regions rather than using an a posteriori statistical modeling procedure to detect elevated prevalence. Statistical inferences about the magnitude and direction of effects drawn from such aggregated data are known to be highly sensitive to the particular grouping chosen (Gehlke and Biehl, 1934; Openshaw and Taylor, 1979). Such groupings may also mask spatial variations at finer scales (Moore and Carpenter, 1999).

This study had a number of limitations. Because we did not have information about the periconceptional address, we used the birth address as an indicator of exposures during pregnancy. Most but not all studies suggest limited exposure misclassification due to residential mobility (Shaw and Malcoe, 1992; Fell et al., 2004; Canfield et al., 2006b; Chen et al., 2010; Lupo et al., 2010). For the subset of the CHD sample for whom we had both the birth and periconceptional addresses ($\sim$ 42% of the total sample), about 15% moved to a different city and/or a different ZIP code during pregnancy.

We may have failed to ascertain all cases of the three CHDs. The defects included in this study were all referred for surgical correction. Because CHW was the only center in Wisconsin surgically correcting congenital cardiac defects during this time period, few infants surviving past the neonatal period would have been missed unless they specifically sought treatment of state. We attempted to limit referral bias to out-of-state facilities by including only ZIP codes from the 44 counties in eastern and central Wisconsin. We did not exclude ZIP codes from counties bordering Illinois, and this may have influenced the observed south-to-north case distribution. It is notable, however, that excluding the 46 ZIP codes within the five Illinois border counties from the analysis for the full sample (data not shown) did not affect the south-to-north gradient for HLHS, TOF, or combined defects.

Cases dying before diagnosis or where parents sought palliative treatment would also have been missed. We identified 27 cases in the Wisconsin death files that could not be probabilistically matched to any of the ascertained cases, and which were not included in the analysis because their diagnoses could not be confirmed by the same methods applied to all other cases (see Methods). Finally, we did not ascertain cases that were terminated, miscarried, or stillborn. These cases are of interest because one of our central concerns is environmental exposures influencing rates of occurrence.

Use of ZIP codes to evaluate demographic associations with disease occurrence has been criticized. As opposed to census units such as blocks, block groups, or census tracts which are constructed to achieve some level of homogeneity with respect to population characteristics, economic status, and living conditions, ZIP codes are large administrative units established to assure efficient delivery of mail (Krieger et al., 2002a; Krieger et al., 2002b). ZIP codes are consequently more heterogeneous and results across analyses may be more inconsistent. It is notable, however, that some investigators have found that, at least for some SES variables, variation within ZIP codes and census tracts is similar (Geronimus and Bound, 1998).

In conclusion, a south-to-north gradient was documented for two of three complex CHDs in eastern Wisconsin. In general, adjustment for ZIP code level census demographic variables did not alter these findings. Further studies controlling for ethnicity, SES, and other person-level risks, and linkage to potential environmental exposures (such as agrichemicals or ground water contamination) are needed to identify risk factors that may underlay this geographic gradient.

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