ORIGINAL RESEARCH

Environmental and Socioeconomic Factors Influence the Live-Born Incidence of Congenital Heart Disease: A Population-Based Study in California

Shabnam Peyvandi (iD), MD, MAS; Rebecca J. Baer, MS; Christina D. Chambers, PhD; Mary E. Norton, MD; Satish Rajagopal, MD; Kelli K. Ryckman, PhD; Anita Moon-Grady, MD; Laura L. Jelliffe-Pawlowski, PhD; Martina A. Steurer, MD, MAS

BACKGROUND: The development of congenital heart disease (CHD) is multifactorial with genetic and environmental influences. We sought to determine the relationship between socioeconomic and environmental factors with the incidence of CHD among live-born infants in California and to determine whether maternal comorbidities are in the causal pathway.

METHODS AND RESULTS: This was a population-based cohort study in California (2007–2012). The primary outcome was having significant CHD. Predictors included socioeconomic status and environmental exposure to pollutants determined by U.S. Census data. A social deprivation index and environmental exposure index was assigned based on neighborhood socioeconomic variables, categorized into 4 quartiles. Quartile 1 was the best with the least exposure to pollutants and social deprivation, and quartile 4 was the worst. Multivariate logistic regression and mediation analyses were performed. Among 2 419 651 live-born infants, the incidence of CHD was 3.2 per 1000 live births. The incidence of CHD was significantly higher among those in quartile 4 compared with quartile 1 (social deprivation index: 0.35% versus 0.29%; odds ratio [OR], 1.31; 95% CI, 1.21–1.41; environmental exposure index: 0.35% versus 0.29%; OR, 1.23; 95% CI, 1.15–1.31) after adjusting for maternal race/ethnicity and age and accounting for the relationship between the 2 primary predictors. Maternal comorbidities explained 13% (95% CI, 10%–20%) of the relationship between social deprivation index and environmental exposure index with the incidence of CHD.

CONCLUSIONS: Increased social deprivation and exposure to environmental pollutants are associated with the incidence of live-born CHD in California. Maternal comorbidities explain some, but not all, of this relationship. These findings identify targets for social policy initiatives to minimize health disparities.

Key Words: congenital cardiac defect ■ environment ■ health disparities ■ socioeconomic position

Congenital heart disease (CHD) is the most common birth anomaly present in 6 to 8 per 1000 live births[1] and is the leading cause of death from a congenital anomaly within the first year of life.[2] A minority of CHD cases (≈20%) can be attributed to known heritable or spontaneous genetic causes such as Mendelian gene defects, chromosomal abnormalities, or pathogenic copy number variants.[3] Thus, the vast majority of CHD cases are thought to be attributed to multifactorial causes including multiple gene interactions and environmental influences. In recent years, it has been shown that social determinants of health contribute to disease and health outcomes and can lead to the development of congenital anomalies.[4–6]

CLINICAL PERSPECTIVE

What Is New?
- We identify both social and environmental factors on the neighborhood level that are associated with the development of congenital heart disease.
- This large study enabled analyses to determine factors in the causal pathway that may explain this association such as maternal comorbidities.

What Are the Clinical Implications?
- The maternal fetal environment can influence the development of birth defects and postnatal outcomes.
- Addressing health disparities and maternal morbidities may lessen the burden of congenital heart defects.

Nonstandard Abbreviations and Acronyms

CHD	congenital heart disease
SDI	social deprivation index
EEI	environmental exposure index
ICD-9-CM	*International Classification of Diseases, Ninth Revision Modification*

Social deprivation and poverty are known to be associated with a multitude of congenital anomalies, including CHD, although the literature is varied.[7–9]

Epidemiological studies have also demonstrated adverse effects of environmental pollutants on health and on the developing fetus.[10,11] Again, however, studies of the relationship of these pollutants with the development of CHD has been inconclusive with inconsistent findings reported.[9,12,13] Furthermore, the mechanisms linking social deprivation and environmental pollutants with the development of CHD is unclear, making it difficult to devise preventive initiatives. A healthy maternal–fetal environment is increasingly recognized as crucial in early fetal development,[14] and maternal comorbidities, such as diabetes mellitus[15] and pregnancy-related hypertensive disorders,[16] have been shown to be associated with the development of CHD in offspring. These comorbidities are also known to be influenced by social determinants of health.[17–20] Thus, maternal comorbidities may in part mediate the relationship between social deprivation, environmental pollutants, and the development of congenital anomalies in offspring.

Our primary aim for this study was to assess the influence of social deprivation and environmental exposure to pollutants on the incidence of live-born CHD in a population-based study in the state of California. Our secondary aim was to determine whether maternal co-morbidities are in the causal pathway between social deprivation and environmental pollution and the development of CHD in offspring. We hypothesized that both social deprivation and environmental pollutants would be associated with live-born CHD and that maternal comorbidities may explain a large percentage of this association.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The California Office of Statewide Health Planning and Development maintains a birth cohort database containing live births from the years 2007 to 2012. This database includes detailed information on linked maternal and infant clinical and demographic characteristics derived from hospital discharge records (maternal hospitalization, birth hospitalization, and readmissions) and birth and death certificates from 1 year prior to birth to an infant age of 1 year. The file provides diagnosis and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The same database has been used by our group to report on a variety of neonatal outcomes.[21,22]

Subjects

We included all live-born infants with gestational ages 22 to 42 completed weeks with valid census tract information (Figure 1). Cases with significant CHD were identified by *ICD-9-CM* diagnostic and procedure codes present in the birth, transfer, or readmission records. Significant CHD was defined as a heart defect requiring or likely to require surgery within the first year of life and included ventricular septal defects with an accompanying procedure code for surgical closure, atrioventricular septal defects, conotruncal defects, transposition of the great arteries, pulmonary atresia/intact ventricular septum, and single ventricle lesions including heterotaxy. A pediatric cardiac intensivist and a pediatric cardiologist (A.M.G., M.A.S.) reviewed all cases according to an a priori framework based on morphogenetically similar developmental mechanisms to ensure correct classification of infants with multiple *ICD-9-CM* codes.[23,24] All *ICD-9-CM* codes were used to determine the presence and type of CHD. Final diagnosis was reached by consensus. Chromosomal anomalies were defined by the *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 758 and included abnormalities detected
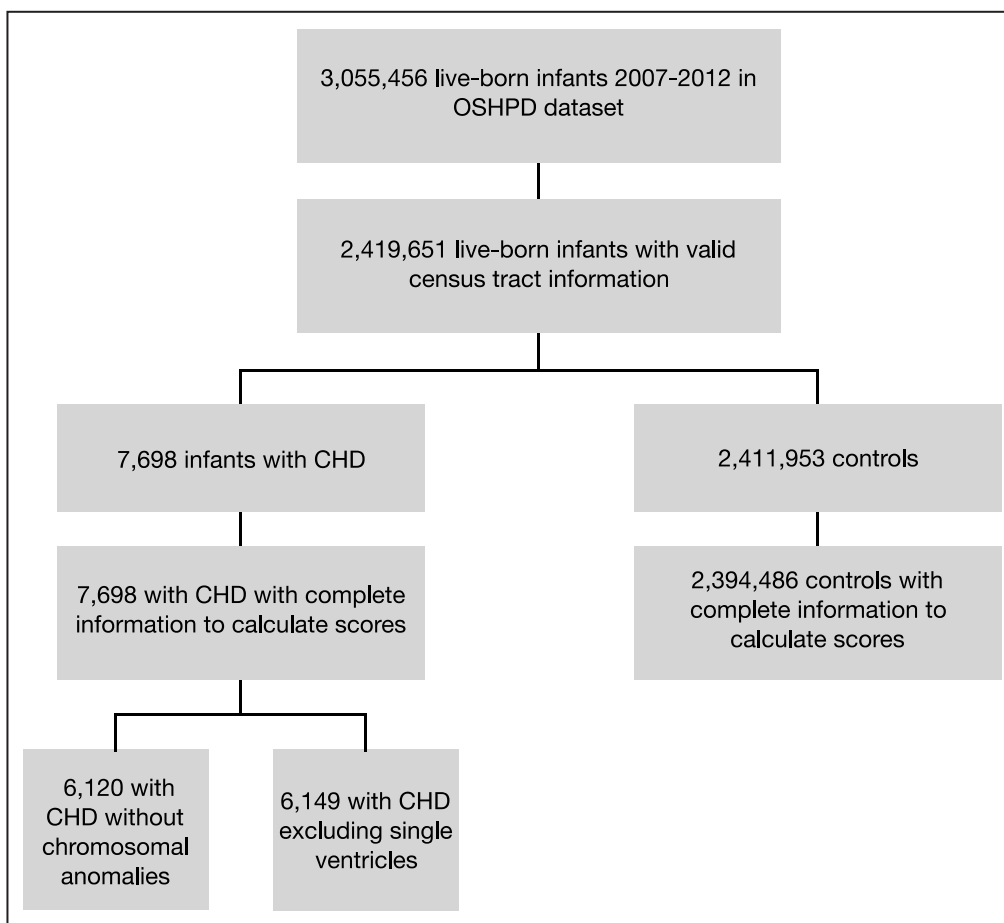
Figure 1. Flowchart of data obtained from the California OSHPD population-based data registry.
CHD indicates congenital heart disease; and OSHPD, Office of Statewide Health Planning and Development.

by karyotype as well as pathogenic copy number variants detected by chromosomal microarray. The control group was defined as those without CHD.

Primary Outcome and Predictors

The primary outcome was the incidence of significant CHD. The main predictors included the social deprivation index (SDI) and the environmental exposure index (EEI) both determined at the neighborhood level. Both indexes were determined based on census tract data of the mother at the time of birth provided by the Office of Statewide Health Planning and Development data set. The SDI was measured using a US Census-based score developed by Diez Roux et al.[25] Socioeconomic variables for each subject's census tract were collected from the US Census website (https://data.census.gov/cedsci/; 2008–2012 American Community Survey 5-year estimates). Based on the method of Diez Roux et al, 6 measures of wealth and income (log of the median household income, log of the median value of housing units, and percentage of households receiving

interest, dividend, or net rental income), education (among adults 25 years of age or older, the percentage who had completed high school, and the percentage who had completed college), and occupation (the percentage of employed people 16 years of age or older in executive, managerial, or professional specialty occupations) were selected to calculate the SDI. For each variable, a Z score for each census group was calculated by subtracting the overall mean (across all block groups in the sample) from the value of the variable for that census group and dividing by the standard deviation. The composite socioeconomic score for each subject was calculated by summing the 6 Z scores (1 for each of the 6 variables) for that subject. This value was then categorized into 4 quartiles with quartile 1 denoting the least social deprivation and quartile 4 the most. The EEI was calculated using similar methodology but using data from the California Communities Environmental Health Screening Tool, version 3.0 (CalEnviroScreen). The CalEnviroScreen 3.0 identifies California communities by census tract that are disproportionately burdened by and vulnerable to multiple

sources of pollution (https://oehha.ca.gov/calenviro-screen/report/calenviroscreen-30). The EEI included levels of exposure to the following pollutants in each census tract: (1) toxic release from facilities, (2) air quality measured by ozone (main ingredient in smog) and particulate matter 2.5, (3) drinking water contaminants, and (4) pollution from diesel engines/exhaust. Similar to the SDI score, Z scores for each pollutant were determined based on the subject's census tract, and the individual Z scores were summed for a summary score. The score was then categorized into 4 quartiles with quartile 1 denoting the least exposure to pollutants and quartile 4 denoting the highest exposure.

Maternal characteristics were collected from the Office of Statewide Health Planning and Development data set and included prepregnancy body mass index (BMI), maternal diabetes mellitus (ICD-9 codes 249, 250, and 648.8), and maternal hypertensive disorders (ICD-9 codes 401–405 and 642). Both pregestational and gestational conditions were collected. Race/ethnicity and age of the mother was self-reported and obtained from the infant's birth certificate record. Missing data were rare in this cohort; however, if a subject had missing data in any variable of interest they were excluded from the analysis.

Statistical Analysis

Descriptive statistics were used to display baseline characteristics of the cohort by the primary outcome (CHD versus control). To test our primary hypothesis, a hierarchical logistic regression analysis clustered by census tract was performed to determine the association between our main predictors and the primary outcome adjusted for maternal race/ethnicity and age for the entire cohort. To determine the relationship between our 2 predictors of interest (SDI and EEI), a new predictor was constructed consisting of the 16 combinations of the EEI and SDI quartiles. A hierarchical logistic regression analysis adjusting for maternal race/ethnicity and age was performed to determine the association between this predictor and the incidence of CHD for each possible combination. Because studies have previously shown a relationship between socioeconomic status and prenatal diagnosis rates,[26] sensitivity analyses were conducted to determine the relationship after excluding severe forms of disease known to have lower birth incidence in regions with high prenatal detection[27,28] (those with chromosomal anomalies or single ventricle heart disease, including heterotaxy). A prespecified significance level was chosen at $P<0.05$.

To test our secondary hypothesis that maternal comorbidities may be in the causal pathway of social deprivation and environmental pollutants with CHD, a formal mediation analysis was performed.

The conceptual model is demonstrated in Figure 2. A mediator is defined as a variable that is on the causal pathway between the predictor and the primary outcome. For this analysis, the SDI and the EEI were summarized to form a total score that was used as a continuous primary predictor. The binary mediator assessed was the presence of any of the following maternal comorbidities: diabetes mellitus, hypertensive disorders, or BMI >25 kg/m^2 versus having no maternal comorbidity. A mediator has to be significantly associated with the predictor and the primary outcome. Both of these conditions were confirmed with simple logistic regression analyses, and the mediation procedures were implemented as previously described.[29] We calculated the total direct and indirect effects mediated by maternal comorbidities in the relationship between SDI and EEI with the incidence of CHD in the entire cohort.

All analyses were performed with STATA version 14.2 (Stata Statistical Software Release 14, Stata Corp LP, College Station, TX). The study was approved by the committee for the Protection of Human Subjects within the California Health and Human Services Agency. Informed consent was waived.

RESULTS

From 2007 to 2012, there were a total of 3 055 456 live-born infants in the state of California, of which 2 419 651 had valid census tract information (79.2%). Among those with valid census tract information, 7698 had significant CHD (live-born incidence of 3.2 per 1000 live births). Figure 1 depicts a flow chart of subjects included for the primary analysis and subanalyses. Crude infant, maternal, and neighborhood characteristics for infants with CHD versus those without CHD are listed in Table 1. Prematurity, small-for-gestational age, and chromosomal anomalies were more common in the CHD group. Maternal factors more common in the CHD group including BMI ≥25 (prepregnancy weight), diabetes mellitus, and hypertensive disorders such as preeclampsia (both pre-existing and pregnancy related). All individual sociodemographic factor Z scores (prior to categorizing into a SDI) were significantly lower in the CHD group compared with the control group. Similarly, environmental exposure Z scores for each individual environmental factor (prior to categorizing into an EEI) were significantly higher in the CHD group compared with the control group.

The adjusted analysis (adjusted for maternal race/ethnicity and maternal age) assessing the primary outcome of live-born CHD incidence revealed several important associations as seen in Table 2. Compared with individuals in the lowest SDI quartile (quartile 1,
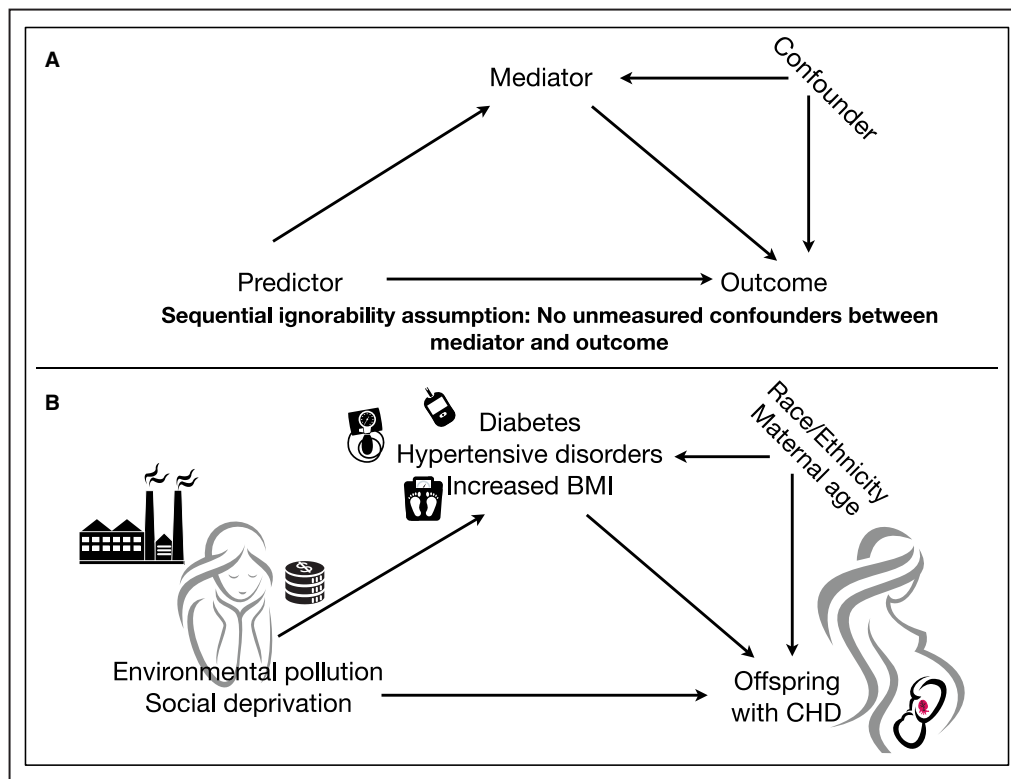
Figure 2.   Conceptual model that formed the basis of the mediation analysis performed.
A, Directed acyclic graph (conceptual analytic model) **B**, The figure demonstrates proposed maternal comorbidities (diabetes mellitus, hypertensive disorders, and increased BMI) that may mediate the relationship between social deprivation and environmental pollution and the incidence of live-born CHD. Also shown are confounders included in the model (maternal race/ethnicity and age). BMI indicates body mass index; and CHD, congenital heart disease.

best socioeconomic status) the odds of live-born CHD was significantly higher among those with increasing exposure to social deprivation (quartiles 2–4). In particular, the odds of CHD was 1.31 times higher (95% CI, 1.21–1.41; $P<0.001$) among those in quartile 4 compared with those in quartile 1. Similarly, compared with individuals with the lowest exposure to environmental pollutants (quartile 1), the odds of CHD was significantly higher among those with increasing exposure to environmental pollutants. The odds of CHD was 1.23 times higher (95% CI, 1.15–1.31; $P<0.001$) among those in quartile 4 compared with quartile 1. The odds of CHD was significantly higher among mothers with 1 or more maternal comorbidities (defined as BMI ≥25, diabetes mellitus, or hypertensive disorder) as compared with those with none.

Figure 3 demonstrates a strong relationship between the SDI and the EEI. For this analysis, the reference group consisted of those in quartile 1 for both environmental exposures and social deprivation. Compared with this reference group, increasing exposure to environmental pollutants and social deprivation was associated with an increased incidence of CHD, suggesting a dose effect. In particular, the

odds of CHD was the highest among those in quartile 4 for both environmental exposures and social deprivation (odds ratio [OR], 1.48; 95% CI, 1.32–1.66; $P<0.001$).

To remove cases of CHD with recognized genetic causality from the data set, a sensitivity analysis was performed excluding those with known syndromic chromosomal anomalies, leaving a total of 6120 infants with CHD in the analysis. Similar findings were noted with a higher incidence of CHD among those in quartile 4 for both environmental exposures and social deprivation compared with those in quartile 1 (Table 2). Given the limitations of this data set in capturing only live-born infants with CHD, the true incidence of CHD accounting for fetal demise and termination by SDI and EEI was not available. To account for this potential differential bias, a second sensitivity analysis was performed excluding subjects with the most severe form of CHD (any single ventricle heart disease) as termination is known to be more prevalent with this fetal diagnosis in select populations.[27,30] Table 2 demonstrates that excluding these subjects (with a remaining sample of 6149 infants with CHD) did not significantly change the association

Table 1. Baseline Characteristics of Infants With CHD versus Infants Without CHD

	CHD	No CHD	P Value*
Sample	n=7698	n=2 411 953	
Infant characteristics (%)			
Gestational age			<0.001
<37 wk	19.1	8.7	
37–38 wk	30.7	27.3	
>38 wk	50.2	64.0	
Birth weight			<0.001
SGA	16.6	8.1	
LGA	8.8	9.5	
Female sex	55.7	51.2	<0.001
Multiple birth	4.7	3.0	<0.001
Chromosomal anomalies	20.1	0.25	<0.001
Maternal characteristics (%)			
Maternal BMI			<0.001
≤25 kg/m^2	46.2	50.6	
≥25 kg/m^2	45.1	42.7	
Missing	8.7	6.7	
Maternal diabetes mellitus			<0.001
Preexisting	3.2	0.8	
Gestational	11.6	8.6	
Maternal hypertensive disorders			<0.001
Preexisting	1.7	1.1	
Gestational	2.3	2.2	
Preeclampsia	5.6	3.8	
Maternal race/ethnicity			<0.001
White not Hispanic	25.1	24.6	
Hispanic	49.5	49.4	
Black	5.6	5.9	
Asian	11.1	12.5	
Other	8.7	7.6	
Maternal age			
<18 y	2.5	2.8	<0.001
18–34 y	74.5	79.0	
>34 y	23.0	18.2	
Neighborhood characteristics by census tract, median (IQR)			
Sociodemographic Z scores			
Adults >25 y who completed high school	−0.20 (−1.19 to 0.59)	−0.13 (−1.09 to 0.61)	<0.001
Adults >25 y who completed college	−0.59 (−1.02 to 0.18)	−0.54 (−0.99 to 0.25)	<0.001
Employed people 16 y of age or older in executive, managerial, or professional specialty occupations	−0.51 (−1.11 to 0.25)	−0.47 (−1.08 to 0.33)	<0.001
Median household income	−0.28 (−0.997 to 0.39)	−0.23 (−0.92 to 0.45)	<0.001
Median value of housing units	−0.20 (−0.93 to 0.37)	−0.14 (−0.83 to 0.46)	<0.001
Households receiving interest, dividend, or net rental income	−0.58 (−1.02 to 0.12)	−0.52 (−0.99 to 0.20)	<0.001
Environmental Z scores			
Toxic release	0.16 (−0.41 to 0.83)	0.12 (−0.42 to 0.82)	0.007
PM 2.5	0.33 (−0.28 to 0.60)	0.33 (−0.45 to 0.60)	<0.001
Ozone	0.046 (−0.36 to 1.0)	0.046 (−0.36 to 0.84)	<0.001
Drinking water	0.38 (−0.42 to 1.43)	0.35 (−0.48 to 0.79)	<0.001
Diesel PM	0.23 (−0.2 to 0.56)	0.24 (−0.19 to 0.57)	0.05

BMI indicates body mass index; CHD, congenital heart disease; IQR, interquartile range; LGA, large for gestational age (>90th percentile); PM, particulate matter; and SGA, small for gestational age (<10th percentile).

*P values from chi-squared test (categorical variables) or 2-sample t test (continuous variables).

Table 2.   Live-Born Incidence and aOR of CHD by Social Deprivation Index, Environmental Exposure Index, and Maternal Conditions

	All CHD (N=7652)		CHD Without Chromosomal Anomalies (N=6120)		CHD Without SV (N=6149)	
	Incidence*	aOR (95% CI)†	Incidence*	aOR (95% CI)†	Incidence*	aOR (95% CI)†
Social deprivation index						
Quartile 1‡	29	Reference	24	Reference	25	Reference
Quartile 2	32	1.16 (1.08–1.24)	25	1.12 (1.04–1.21)	26	1.11 (1.03–1.20)
Quartile 3	32	1.18 (1.10–1.27)	26	1.16 (1.07–1.26)	25	1.13 (1.04–1.22)
Quartile 4	35	1.31 (1.21–1.41)	27	1.25 (1.15–1.36)	27	1.23 (1.13–1.34)
Environmental index						
Quartile 1‡	29	Reference	23	Reference	24	Reference
Quartile 2	31	1.09 (1.02–1.16)	25	1.09 (1.01–1.17)	25	1.03 (0.96–1.11)
Quartile 3	32	1.11 (1.04–1.19)	26	1.12 (1.04–1.21)	26	1.07 (0.99–1.16)
Quartile 4	35	1.23 (1.15–1.31)	28	1.24 (1.15–1.33)	27	1.16 (1.08–1.25)
Maternal conditions§						
None	28	Reference	22	Reference	22	Reference
1	31	1.12 (1.06–1.18)	25	1.11 (1.05–1.18)	25	1.14 (1.07–1.20)
2	45	1.56 (1.44–1.68)	36	1.60 (1.47–1.74)	36	1.55 (1.43–1.69)
3	64	2.20 (1.88–2.56)	55	2.44 (2.07–2.89)	53	2.23 (1.88–2.65)

Results of the sensitivity analyses are also shown when excluding those with chromosomal anomalies or those with single ventricle heart disease. aOR indicates adjusted odds ratio; CHD, congenital heart disease; and SV, single ventricle.

*1/1000 live births.

†Adjusted for maternal race/ethnicity and maternal age.

‡Quartile 1 is the most favorable and quartile 4 is the least favorable.

§Maternal conditions: body mass index >25 kg/m^2, hypertensive disorder (preexisting and pregnancy induced hypertension, preeclampsia), diabetes mellitus (preexisting and gestational).

between the SDI and EEI with the incidence of CHD. Specifically, the odds of CHD was the highest among those in quartile 4 for both environmental exposures and social deprivation (OR, 1.23; 95% CI, 1.13–1.34; $P<0.001$) even after excluding those with single ventricle heart disease.

% of population aOR (95% CI)		Social Deprivation Index			
		1st quartile (best)	2nd quartile	3rd quartile	4th quartile (worst)
Environmental Exposure Index	1st quartile (best)	9.3% reference	7.5% 1.21 (1.07-1.37)	4.8% 1.12 (1.06-1.40)	3.4% 1.26 (1.07-1.48)
	2nd quartile	8.3% 1.12 (0.99-1.26)	6.6% 1.28 (1.13-1.45)	6.3% 1.26 (1.11-1.42)	3.9% 1.41 (1.23-1.61)
	3rd quartile	5.1% 1.14 (0.99-1.30)	5.4% 1.21 (1.05-1.39)	7.0% 1.26 (1.10-1.44)	7.6% 1.45 (1.29-1.64)
	4th quartile (worst)	2.3% 1.25 (1.04-1.50)	5.5% 1.39 (1.23-1.56)	6.9% 1.41 (1.24-1.59)	10.1% 1.48 (1.32-1.66)

Figure 3.   The interplay between environmental exposures and social deprivation in the incidence of congenital heart disease.
Quartile 1 represents the least exposure to environmental pollutants and the least social deprivation. The percent of the entire population in each quadrant is presented along with the odds of congenital heart disease compared with the reference category (quartile 1 for both environmental and social deprivation index) after adjusting for maternal race/ethnicity and age.

The final analysis performed aimed to determine whether the maternal comorbidities known to be associated with the development of CHD can act as mediators between our primary predictor and outcome (Figure 2). The causal mediation analysis showed that 13% (95% CI, 10%–20%) of the total effect of SDI/EEI on the incidence of CHD is mediated through the presence of 1 or more maternal comorbidities with maternal race/ethnicity and age in the model as confounders in the relationship between maternal conditions and the incidence of CHD.

DISCUSSION

In this large population-based sample from the state of California, we demonstrate the influence of socioeconomic factors and exposures to environmental pollutants on the incidence of live-born, clinically significant CHD. In particular, increasing exposure to social deprivation and environmental pollutants was associated with an increased live-born incidence of CHD in offspring. Some, but not all, of this association is explained by maternal comorbidities, suggesting other potential pathways for the role of the maternal environment in the formation of CHD in offspring.

The study of social determinants of health has revealed that social disadvantage plays a significant role in health outcomes for a variety of conditions[31] even in developed countries. In the field of congenital cardiology, social determinants of health are known to influence short-term and long-term outcomes.[22,32] However, the role of social determinants in the development of congenital anomalies is less well understood.[4] In particular, the influence of socioeconomic position or social deprivation on the incidence of CHD is not well documented. socioeconomic variables measured at the individual level such as maternal education, income, and insurance status from large administrative databases have revealed an association with the incidence of live-born CHD, although the opposite has been reported as well.[8,33–36] In contrast, measuring socioeconomic position at a neighborhood level has yielded different results. A large population-based study in Sweden demonstrated that the incidence of live-born CHD was higher in deprived neighborhoods.[37] This inconsistency may in part be related to differing methodologies in measuring socioeconomic position. Although individual-level measures are reflective of socioeconomic position across an individual's lifespan, some studies suggest that neighborhood socioeconomic position is a more comprehensive measure and may predict health outcomes above and beyond individual factors.[38] In our study, lower socioeconomic position at the neighborhood level was found to be associated with the incidence of live-born CHD and was most significant for those with the highest social deprivation. Similar to socioeconomic position, there is a large body of literature linking toxic environmental agents to several health outcomes including prematurity, low birth weight, and congenital anomalies.[39] Most studies have concluded that environmental toxins, especially particulate matter, residence near hazardous waste and agricultural chemicals (as measures of air pollution) are associated with the development of congenital anomalies including CHD,[13,40–43] though some have found no association.[12] Consistent with prior studies, our data also demonstrates that higher exposure to environmental pollutants is associated with an increased incidence of CHD.

Our analysis on the relationship between the 2 main predictors (environmental pollutants and socioeconomic status) demonstrates the difficulty in disentangling the health effects of social disadvantage. Our data demonstrate that exposures to toxic pollutants is highest among those with the highest social deprivation. The concept of environmental injustice stems from the fact that there are racial and socioeconomic disparities in pollution exposure.[44] Despite several local and federal programs aimed at minimizing these disparities, several studies, including ours, suggest that they still exist,[39,45–47] providing potential targets for social policy initiatives.

Maternal conditions such as diabetes mellitus, hypertension, and preeclampsia are associated with CHD.[15,16] In addition, it is well known that these conditions are disproportionately higher in deprived communities and among individuals of lower socioeconomic status.[18–20] Thus, we hypothesized that maternal comorbidities may explain part of the association between socioeconomic status and the incidence of CHD. Our mediation analysis suggests that 13% of the relationship between social deprivation and environmental pollution and CHD can be explained by these specific maternal comorbidities. Although we adjusted for potential confounders in the formal mediation analysis that were available to us in this data set (ie, maternal age and race/ethnicity), there is a possibility of unmeasured confounders that can influence our findings. Thus, it is difficult to establish causality even when conducting a formal mediation analysis using an administrative database. The mechanisms explaining our findings appear to be more complicated and potentially related to other pathways connecting environmental toxins and social deprivation to conditions that affect the developing fetus. There is a growing body of literature on the adverse effects of social deprivation and maternal stress on the developing fetus.[48–50] It is thought that epigenetic mechanisms modify crucial enzyme activity at the placental level altering transmission of stress hormones to the developing fetus.[51] Although

much of this work has been focused on the effects on neurodevelopmental outcomes in offspring,[52,53] epidemiological studies suggest a role of maternal stress in the development of fetal anomalies.[54,55] Although we did not directly measure maternal stress levels in this study, social deprivation acts as a significant stressor and could be a potential explanation for the association found in our study.

The biological mechanism linking environmental toxins to the formation of anomalies in offspring is largely unknown, although several hypotheses have been formulated based on animal studies. Studies in mice have suggested that exposures to organic solvents, for example, can induce oxidative stress and alter cardiac morphogenesis.[56] Importantly, the placenta is a key organ that acts as the gatekeeper between the environment and the fetus. Genetic variations in placental enzymes (such as glutathione S-transferases) may promote transmission of harmful toxins leading to fetal developmental anomalies, including CHD.[57,58] Finally, epigenetic modification of DNA in the placenta and/or fetus from exposure to toxins may influence heart development.[59,60]

There are some notable limitations to our study. First, in any administrative database there is the possibility of incorrect ascertainment of diagnoses using ICD-9 codes and/or misclassification of diagnoses. However, cases were captured from multiple sources including birth hospitalization, transfer records, and readmission records during the first year of life. In addition, 2 physicians independently reviewed every case with multiple codes for CHD. Despite this limitation, the incidence of significant CHD in our study is similar with previous population based studies.[1] Second, ≈20% of the data were excluded because of a lack of valid census tract information. Third, our study only assessed the incidence of live-born CHD. We were unable to capture the true incidence of CHD including fetal demise or termination of pregnancy. Pregnancy loss is higher in anomalous fetuses and was not able to be accounted for in this data set. With increased detection of CHD prenatally, the live-born incidence of CHD has decreased as a result of elective terminations.[27,28,30] Pregnancy termination rates may in turn be influenced by socioeconomic position either directly or as a result of the influence of socioeconomic position on access to prenatal care. We would only expect differential selection bias and an attenuation of our association if elective terminations were more likely among those with a higher socioeconomic status. Interestingly, studies from other countries have noted no difference in termination patterns based on maternal age, occupation, and place of residence when there is a prenatal diagnosis of CHD.[28,61] However, to account for any possible differential selection bias attributed to pregnancy termination, we performed a sensitivity analysis and excluded subjects with any single ventricle heart disease, which has previously been shown to have a lower than expected birth incidence in regions with high prenatal detection rates,[27] and our results remained significant. Finally, there is a potential for exposure misclassification when measuring environmental pollutants. The study of environmental agents is inherently challenging and prone to residual confounding given the difficulty in measuring other environmental toxins such as smoke exposure; however, this would only be expected to underestimate our findings. In addition, we used the CalEnviroScreen data, which use objective data relating to pollution sources, releases, and environmental concentrations as indicators of potential human exposures to pollutants. The timing of exposure to environmental pollutants is also an important factor and a potential limitation of our study. In our study, we used the census tract data from the birth certificate and thus made the assumption that the census tract reflected the mother's environment at the time of conception and early fetal development.

Despite these limitations, there are strengths to our study. First, we used a large population-based dataset in the state of California, which has a diverse socioeconomic profile. Conceptually, our study may be generalizable to other regions within the United States; however, it is possible that these findings may vary in other states with differing socioeconomic and environmental profiles than California. Second, we relied on census-tract data, which minimizes recall bias when reporting exposures. Finally, we assessed the complex relationship between social deprivation and environmental influences on our primary outcome, which was possible because of the large sample size of our cohort.

In conclusion, both social deprivation and environmental pollutant exposure are associated with an increased incidence of CHD among live-born infants. Maternal comorbidities explain a small but significant percentage of this association. Our findings further strengthen the notion that environmental injustice exists and that social policy initiatives to decrease the burden of CHD should focus on minimizing exposures to harmful toxins in socioeconomically deprived regions. In addition to large organizations attempting to modify environmental policies to minimize these social disparities, engagement with at-risk communities is key to empower those affected to influence policy change.[62] Research is needed to determine whether community engagement and outreach to at-risk communities can allow for the identification of exposures and other risk factors and the development of feasible and cost-effective interventions to lessen health disparities.

ARTICLE INFORMATION

Affiliations

From the Divisions of Critical Care (S.R., M.A.S.) and Cardiology, Departments of Pediatrics (S.P., A.M.-G.) and Epidemiology and Biostatistics (S.P., L.L.J.-P., M.A.S.), Obstetrics, Gynecology and Reproductive Sciences (R.J.B., M.E.N.), and California Preterm Birth Initiative (R.J.B., L.L.J.-P., M.A.S.), University of California San Francisco Benioff Children's Hospital, San Francisco, CA; Department of Pediatrics, University of California San Diego, La Jolla, CA (R.J.B., C.D.C.); Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA (K.K.R.).

Disclosures

None.

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