Potential Impact of Maternal Nighttime Light Exposure and Its Interaction With Sociodemographic Characteristics on the Risk of Various Congenital Heart Diseases

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Background: Although maternal exposure to artificial light at night has shown negative associations with pregnancy outcomes, its impact on the risk of congenital heart disease remains unclear. This study examined the association between maternal exposure to artificial light at night during pregnancy and occurrence of congenital heart disease in offspring, considering potential interactions with sociodemographics.

Methods: We included newborns diagnosed prenatally with congential heart disease and healthy volunteers from 21 cities in southern China. Using satellite data, we estimated annual exposure to artificial light at night at maternal residential addresses during pregnancy. We evaluated associations using marginal structural logistic models and assessed multiplicative and additive interaction between sociodemographics and light exposure.

Results: Each 1-unit increase in light at night during pregnancy was associated with an elevated risk of total congenital heart disease (odds ratio [OR]: 1.2, 95% confidence interval [CI]: 1.2, 1.3), and of almost all specific disease subtypes, in offspring. Using quartiles of light at night confirmed a monotonic dose–response relationship between exposure and disease. The association was more pronounced in severe disease. Some sociodemographic characteristics modified associations between light at night and congenital heart disease, with detrimental associations more pronounced among offspring

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of mothers with lower education (OR: 1.3, 95% CI: 1.2, 1.3), lower income (OR: 1.2, 95% CI: 1.1, 1.3), or being usual residents (OR: 1.3, 95% CI: 1.2, 1.4), based on the continuous model.

Conclusions: Maternal exposure to artificial light at night during pregnancy was substantially associated with an elevated risk of congenital heart disease in offspring. This association was more pronounced among some sociodemographic groups.

Keywords: Adverse pregnancy outcome; Artificial light at night (ALAN); Congenital heart disease (CHD); Interaction; Light pollution; Sociodemographics

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INTRODUCTION

Congenital heart disease (CHD) constitutes one-third of congenital anomalies,[1] representing the most prevalent type of congenital malformation present at birth. Among congenital abnormalities, the global prevalence of CHD was 8.22‰, with the reported rate in China being 4.905‰ in 2015–2019.[2] CHD stands as a prominent cause of disability and death among infants. It is estimated that the prevalence among infants is 1%, and the mortality rate constitutes 6% of infant deaths.[3] This condition substantially affects individuals, families, and society. Moreover, CHD imposes a substantial economic burden worldwide. Hospitalization costs for CHD surpassed $6 billion in the United States in 2013,[4,5] while during the period from 2018 to 2020 in China, the median costs were ¥62,014 (approximately 8,991 USD), ¥64,846 and ¥67,867,[6] with a rising trend. Therefore, CHD has emerged as an important public health challenge worldwide.[7]

Although the etiology of CHD is still unclear, previous research has indicated that genetic factors and environmental exposures significantly contribute to its development.[8] Numerous previous studies have investigated the relationship between environmental exposures and CHD. For example, a recent comprehensive review examined the link between prenatal air pollution exposures and risk of CHD.[9]

Artificial light at night (ALAN) is also an important part of our physical environment. The extent of global land illuminated by ALAN has experienced a remarkable increase in recent decades. The total brightness of the Earth increases by 1.8% annually with China being the fastest growing country in nighttime luminosity worldwide (6.48% per year).[10] Numerous studies have reported that increased light at night exposure is correlated with various adverse health outcomes, including cardiovascular disease,[11] obesity,[12] mental health disturbances,[13] sleep disorders,[14] and cancer.[15] Although existing evidence on the association between ALAN during pregnancy and the risk of CHD is very limited, such association is biologically plausible. First, ALAN could disrupt the circadian rhythms of pregnant women.[16] The regulation of circadian rhythms during pregnancy is essential for normal maternal and fetal physiological processes,[17] potentially affecting the fetal heart. Second, exposure to ALAN influences maternal hormone levels, particularly melatonin, a hormone crucial for regulating circadian rhythms during pregnancy.[18] This could impact nutrient delivery to the fetus,[19] which may alter the developmental pathways of the fetal heart. Third, exposure to ALAN during pregnancy could affect the development of the daily rhythm of key hormonal and metabolic signals in the fetus.[20] These essential hormone levels are vital for organ maturation, including the development of the heart. Recent research has found that exposure to ALAN could subsequently influence pregnancy outcomes such as preterm birth,[21] macrosomia, and large abdominal circumference.[22] Nonetheless, it is unclear whether maternal exposure to ALAN could affect the development of CHDs in the offspring. Understanding the relationship between maternal exposure to ALAN and CHD from a multidimensional perspective could offer valuable insights for reducing the burden of these diseases in offspring.

To address this critical knowledge gap, our study investigated the relationship between maternal exposure to ALAN during pregnancy and the development of CHD and its distinct subtypes in offspring. We also comprehensively explored the potential interactions between maternal exposure and sociodemographics and identified high-risk groups. Sociodemographics may influence exposure to environmental factors, healthcare access, lifestyle choices, and overall health status. This study was based on data from the Guangdong Congenital Heart Disease Registry (GRCHD), a comprehensive and extensive case and control tracking system developed in southern China.

METHODS

Study design and population

In this case–control study, the cases were identified from the GRCHD, which is the largest CHD registration system in China. The GRCHD is an ongoing registry spanning 40 centers across 21 cities in Guangdong Province, southern China. The study included births from 2004 to 2022. Controls were singleton newborns without congenital malformations, frequency-matched to cases based on the residence (i.e., the same city and town), the week of conception, and the hospital where the infants were born, following the idea in previous studies.[23–25] Among the 40 centers, two were prenatal diagnosis centers that could identify cases during prenatal screening but could not ascertain controls (i.e., fetuses ultimately born healthy), resulting in very limited controls. To ensure the generalizability, all centers were retained in the main analyses. At enrollment, trained obstetric nurses conducted face-to-face interviews using a standardized questionnaire to collect information, including maternal baseline information, general sociodemographics, pregnancy characteristics, history of environmental and occupational exposures, and basic information about the offspring. Informed consent was obtained from all participants included in the study. Our study received approval

from the Human Subjects Committees of Guangdong General Hospital (No. GDREC2011135H).

Outcome definition

We identified cases using the International Classification of Diseases (ICD-10: Q20.000-Q28.000) codes. All fetuses, with or without CHD, underwent assessment by obstetricians, pediatricians, and pediatric cardiologists shortly after birth. Each echocardiogram of the heart disease cases was evaluated separately by two echocardiologists. The diagnosis of CHD was then confirmed by a computed tomography scan, cardiac catheterization, autopsy, or surgery. Following the classification methods proposed by Botto et al.[26] and Øyen et al.,[27] we categorized CHD into various subtypes based on etiology. These subtypes included conotruncal defects, anomalous pulmonary venous return, atrioventricular septal defects, right ventricular outflow tract obstruction, left ventricular outflow tract obstruction, single ventricle (SV), septal defects, and other congenital heart malformations. We also cases were also grouped into subtypes based on disease severity. We defined patients with cyanotic conditions or SV physiology as severe CHD, while all others as nonsevere CHD, which included moderate (i.e., requiring more than one operation but excluding the severe ones) and mild CHD (i.e., with conditions necessitating no more than one surgical or transcatheter intervention). We initially included a total of 29,893 fetuses (6,693 cases from the two prenatal diagnosis centers and 12,820 cases from others, with a participation rate of 100%; 20 controls from the two centers and 10,360 controls (12,820 invited) from others, with a participation rate of 81%). Following the exclusion criterion (Figure 1), we included 9,764 CHD cases and 8,488 controls in our final analysis. To assess potential selection bias due to nonparticipation, we compared the baseline characteristics of individuals included in the final analysis with those being excluded, after removing records with missing baseline data.

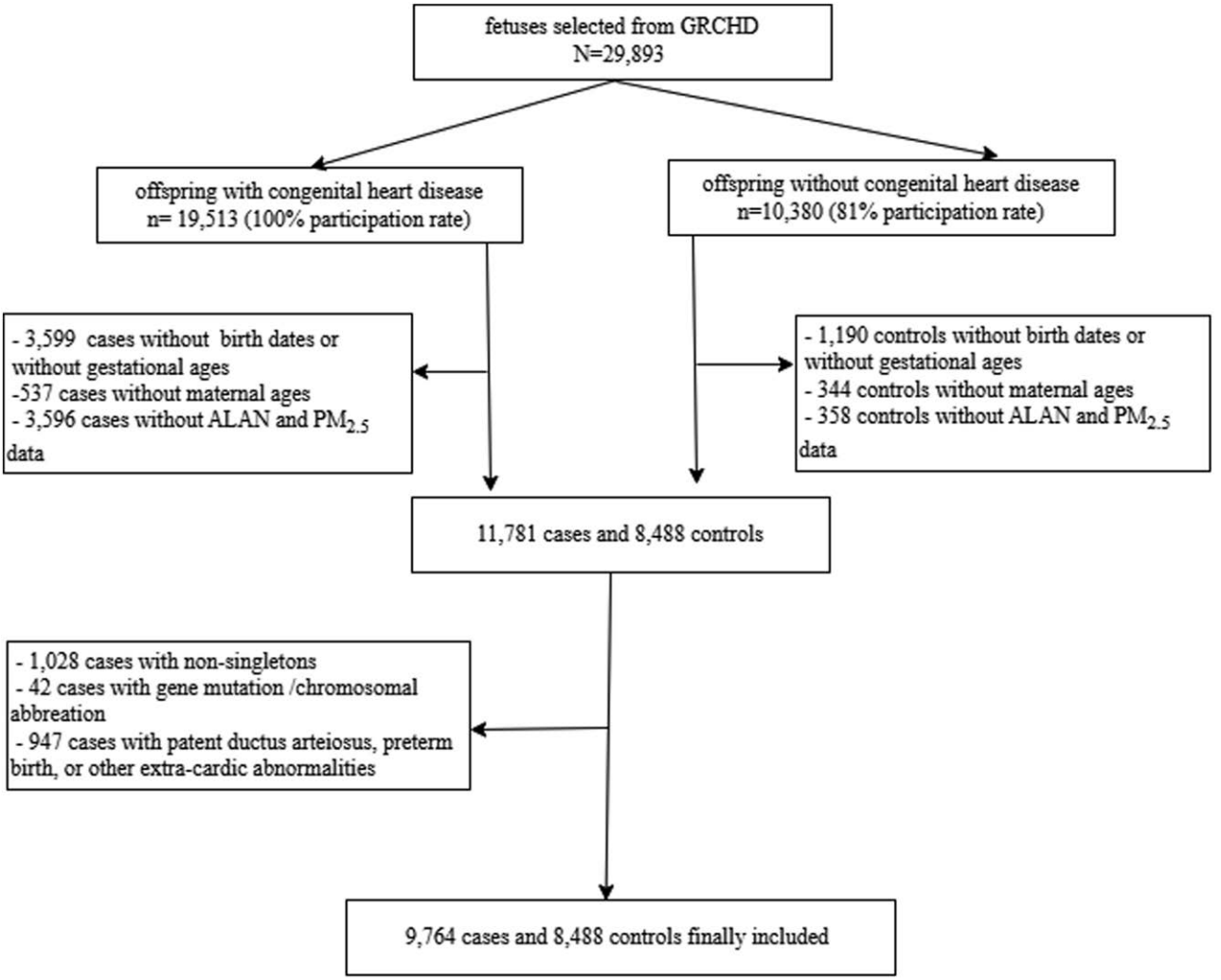

FIGURE 1. Flow chart of study participant selection. CHD indicates congenital heart defects; ALAN, artificial light at night; GRCHD, Guangdong Congenital Heart Disease Registry.

The characteristics of the included and excluded participants are similar, as presented in eTable S1; https://links.lww.com/EDE/C250.

Assessment of artificial light at night

We obtained nighttime light data from the National Earth System Science Data Center of China. The nighttime dataset was generated using a cross-sensor nighttime light data correction scheme based on autoencoders for Defense Meteorological Satellite Program-Operational Linescan System and National Polar-Orbiting Partnership's Visible Infrared Imaging Radiometer Suite (NPP-VIIRS) proposed by Chen et al.[28] It covers global nighttime light data from 2000 to 2022 with a resolution of 500 m. Chen et al. input 2013 Enhanced Average Nighttime Light Index data into an autoencoder and used the same year's NPP-VIIRS composite nighttime light data as the validation set for iterative training. This process successfully generated the "NPP-VIIRS-like" nighttime light dataset (NPP-VIIRS-like NTL Data). The NTL dataset used in this study underwent rigorous validation which showed a strong agreement of the data with the well-established NPP-VIIRS data, with pixel-level R^2 consistently greater than 0.7 across randomly selected pixels. This dataset has been used in multiple previous studies.[29,30] The light at night data is measured as the mean radiance in nanowatts per square centimeter per steradian (nW/cm^2/sr), which represents the amount of light energy emitted or reflected per unit area and solid angle. We geocoded maternal residential addresses and estimated maternal exposure to ALAN by extracting the average exposure within 500-m buffers around the residential address from raster maps of the annual ALAN values for the year of pregnancy. ALAN data were also available from 2000 to 2022, fully overlapping with our study period.

Statistical analysis

We used a marginal structure logistic regression model to assess the relationship between maternal exposure to ALAN during pregnancy and CHD in offspring. In observational studies, causal inference methods aim to estimate counterfactuals, which represent the potential outcomes that might have occurred if individuals had been exposed to different conditions. The marginal structural model achieves this objective by employing inverse probability weighting (IPW) within a counterfactual framework to construct a weighted pseudo-population. This approach serves as a formal causal modeling technique widely used in observational studies.[31] The pseudo-population generated through the IPW method achieves balance across all measured covariates, making it particularly suitable for our large-scale population-based case–control study.

Initially, by regressing the exposure against the potential confounders, we created a generalized propensity score. Subsequently, we developed a stable IPW based on the generalized propensity score to create a weighted pseudo-population.[31] To ensure the robustness of our results, we estimated the weights using three different methods—linear models,[32] generalized estimating equations,[33] and gradient boosting machine learning,[34] and incorporated them into marginal structural logistic models. We assessed the balance of confounders by evaluating the mean absolute correlation on the weighted pseudo-population. An absolute correlation value below 0.1 indicates a high-quality of confounding balance, thus, an enhanced interpretability and validity of our estimates.[35] Finally, we used the linear model-IPW method, which achieved the optimal balance of confounders (as shown in eFigure S1; https://links.lww.com/EDE/C250) for the final model. To select the minimal sufficient adjustment sets, we employed directed acyclic graphs (as seen in eFigure S2; https://links.lww.com/EDE/C250), finally considering maternal age (<35/≥35), maternal ethnicity (Han/others), household income (≤2,500 yuan/2,501–5,000 yuan/>5,000 yuan), maternal education level (high school or below/university or higher), pregnancy season (spring/summer/autumn/winter), active smoking (yes/no), residence location (urban/rural), migrant status (usual resident: persons residing in the area for ≥6 months/migrant: persons residing in the area for <6 months, following the definition by the National Bureau of Statistics of China),[36] temperature, and $PM_{2.5}$ as potential confounders. We addressed missing confounder data (missing rates <5%) using multiple imputations via a chained equation approach,[37] which was commonly used in previous studies.[38–40]

Overall, we developed four models in our study as follows: Model 0: The traditional logistic regression was employed as the crude model. Model 1: An age-adjusted model. Model 2: Further adjusted for potential confounders, including maternal ethnicity, household income, maternal education level, season of pregnancy, active smoking, residence location, migrant status, temperature, and $PM_{2.5}$. Model 3: Essentially a refinement of Model 2 utilizing a marginal structural logistic model with IPW based on the linear model. Model 3 was considered as the primary model in this study. We analyzed exposure to ALAN was analyzed as both a continuous variable and a categorical variable divided into quartiles, that is, Q1 (lowest; 0–3.4 nW/cm^2/sr, n = 4,562), Q2 (3.4–15.1 nW/cm^2/sr, n = 4,564), Q3 (15.2–26.8 nW/cm^2/sr, n = 4,563), and Q4 (highest; 26.8–97.5 nW/cm^2/sr, n = 4,563), with Q1 serving as the reference group.

Additionally, based on Model 3, we conducted stratified analyses by maternal education level, residence location, maternal age, household income, and migrant status. We assessed the interaction between ALAN and sociodemographic characteristics, both on multiplicative and additive scales. We evaluated multiplicative interactions using *P*-values for interaction that we calculated by comparing models with and without the product term of ALAN exposure and sociodemographic factors. Additionally, additive interaction was

analyzed through the calculation of the relative excess risk due to interaction (RERI), a well-established metric in epidemiology for quantifying the combined effects of two exposures.[41] The variance and 95% confidence intervals (CIs) of RERI were estimated using the delta method.[42] In this framework, RERI values are interpreted as follows: 0 indicates no interaction, values >0 suggest positive additive interaction, and values <0 denote negative additive interaction.[43]

We conducted several sensitivity analyses to ensure the reliability of the results including employing the 1000-m buffer instead of the 500-m buffer in light-at-night exposure calculation, or excluding participants who had lived in a newly renovated home within 6 months before childbirth or experienced gestational hypertension or diabetes. Although these factors are not typically considered primary confounders in the relationship between ALAN and CHD, they represent potential sources of bias that could influence the risk of disease through chemical-induced developmental toxicity and maternal metabolic-vascular dysfunction[44–46] Further, we reran models based on the original nonimputed data or excluding the participants from the two prenatal diagnosis centers to further confirm the reliability of the findings. Finally, to assess the robustness of our findings against potential unmeasured confounding, we calculated *E*-values for three marginal structural logistic models in the analysis of overall CHD.[47]

RESULTS

Maternal and fetal characteristics

Comparing maternal characteristics between the case and control groups, mothers in the case group were more likely to be older than 35 years (15% vs. 10%), have a monthly household income of less than 2,500 yuan (37% vs 40%), and smoke during pregnancy (1% vs. 0.3%) (Table 1). Similarly, alcohol consumption during pregnancy was higher among mothers in the case group (0.7% vs. 0.3%). Additionally, a higher proportion of mothers in the case group lived in newly renovated homes (3% vs 0.8%).

Further, we examined the demographic characteristics based on levels of exposure to ALAN (eTable S2; https://links.lww.com/EDE/C250) and assessed the distribution of exposure across different sociodemographic subgroups (eFigure S3; https://links.lww.com/EDE/C250).

TABLE 1. Maternal and Fetal Characteristics

Characteristics	Missing Proportion	N = 18 252 (%)	
		Cases = 9764	Controls = 8488
Maternal age			
<35	4%	8,342 (85)	7,656 (90)
≥35		1,422 (15)	832 (10)
Maternal ethnicity			
Han	0.6%	9,574 (98)	8,387 (99)
Others		190 (2)	101 (1)
Residence location			
Urban	3%	6,336 (65)	5,464 (64)
Rural		3,428 (35)	3,024 (36)
Migrant status			
Migrant	3%	2,102 (22)	1,718 (20)
Usual resident		7,662 (78)	6,770 (80)
Household income			
≤2500	5%	3,655 (37)	3,401 (40)
2501–5000		4,248 (44)	3,786 (45)
>5000		1,861(19)	1,301 (15)
Maternal education level			
High school or below	2%	7,512 (77)	6,383 (75)
University or higher		2,252 (23)	2,105 (25)
Fetal sex			
Male	1%	5,561 (57)	4,817 (57)
Female		4,203 (43)	3,671 (43)
Pregnancy season			
Spring	0%	2,427 (25)	2,142 (25)
Summer		2,315 (24)	1,982 (23)
Autumn		2,361 (24)	2,102 (25)
Winter		2,661 (27)	2,262 (27)
Active smoking			
Yes	0.4%	109 (1)	27 (0.3)
No		9,655 (99)	8,461 (99.7)
Active drinking			
Yes	0.3%	70 (0.7)	25 (0.3)
No		9,694 (99.3)	8,463 (99.7)
Passive smoking			
Yes	0.4%	1,254 (13)	991 (12)
No		8,510 (87)	7,497 (88)
Living in a newly renovated room			
Yes	0.9%	266 (3)	72 (0.8)
No		9,498 (97)	8,416 (99.2)

Association between maternal exposure to artificial light at night during pregnancy and congenital heart disease in newborns

Tables 2 and 3 show associations between maternal exposure to ALAN during pregnancy and specific subtypes of CHD in the offspring. We observed an association between light at night exposure during pregnancy and an elevated risk of total CHD in fetuses (odds ratio [OR]: 1.2, 95% CI: 1.2, 1.3, each 1-unit increase in exposure), as described in Table 2. Moreover, maternal exposure to ALAN during pregnancy was linked to an increased risk of most CHD phenotypes, with the exception of SV and truncus arteriosus. Notably, for each 1-unit increase in exposure, the highest risk was observed for double outlet right ventricle (OR: 2.6; 95% CI: 1.9, 3.5), followed by pulmonary atresia (OR: 1.9; 95% CI: 1.4, 2.5) and coarctation of the aorta (OR: 1.8; 95% CI: 1.4, 2.3). In Table 3, the association was even stronger for severe CHD (OR: 1.6; 95% CI: 1.4, 1.8) compared to nonsevere cases (OR: 1.1; 95% CI: 1.1, 1.2), each 1-unit increase in exposure.

When we divided to ALAN into quartiles (Table 4), the three higher quartiles (2, 3, and 4) were linked to an increased

TABLE 2. Association Between Maternal ALAN Exposure During Pregnancy (1-unit Increase, nW/cm²/sr) and the Risk of CHD and Its Subtypes in Offspring

		Model 0	Model 1	Model 2	Model 3
CHD Phenotypes	**N**	**OR**	**OR**	**OR**	**OR**
Total CHDs	9,764	1.2 (1.2–1.3)	1.2 (1.2–1.3)	1.2 (1.2–1.3)	1.2 (1.2–1.3)
Conotruncal defect	760	1.4 (1.2–1.6)	1.4 (1.2–1.5)	1.4 (1.3–1.6)	1.5 (1.4–1.7)
Truncus arteriosus	51	0.68 (0.41–1.1)	0.67 (0.41–1.1)	0.79 (0.47–1.3)	0.77 (0.50–1.2)
TGA	293	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.6 (1.3–1.9)	1.5 (1.3–1.8)
DORV	91	1.7 (1.2–2.3)	1.7 (1.2–2.3)	1.5 (1.1–2.5)	2.6 (1.9–3.5)
TOF	325	1.4 (1.1–1.6)	1.3 (1.1–1.6)	1.4 (1.1–1.7)	1.5 (1.3–1.8)
LVOTO	500	1.7 (1.4–2.1)	1.7 (1.4–2.0)	1.6 (1.3–1.9)	1.7 (1.4–2.0)
IAA	233	1.8 (1.5–2.2)	1.8 (1.5–2.2)	1.6 (1.3–2.0)	1.8 (1.4–2.3)
vAS	37	1.2 (0.74–2.0)	1.2 (0.73–2.0)	1.4 (0.80–2.3)	1.2 (0.74–2.0)
HLHS	44	1.4 (0.88–2.2)	1.4 (0.86–2.1)	1.3 (0.78–2.1)	1.4 (0.90–2.1)
CoA	186	1.9 (1.5–2.3)	1.9 (1.5–2.3)	1.7 (1.3–2.1)	1.8 (1.4–2.3)
APVR	90	1.7 (1.2–2.3)	1.7 (1.2–2.3)	1.8 (1.2–2.5)	1.6 (1.2–2.2)
PAPVC	17	1.2 (0.57–2.5)	1.2 (0.57–2.5)	1.7 (0.79–3.7)	1.6 (0.94–2.6)
TAPVC	73	1.8 (1.3–2.5)	1.8 (1.3–2.5)	1.8 (1.3–2.6)	1.7 (1.2–2.3)
RVOTO	539	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.6)
Ebstein anomaly	24	1.4 (0.75–2.5)	1.4 (0.75–2.5)	1.2 (0.61–2.3)	1.2 (0.65–2.2)
TA	67	1.5 (0.75–3.1)	1.5 (0.72–3.0)	1.6 (0.76–3.4)	1.6 (0.87–3.0)
HRHS	53	1.6 (1.1–2.4)	1.6 (1.1–2.4)	1.7 (1.1–2.5)	1.5 (1.0–2.1)
PA	98	1.6 (1.2–2.2)	1.6 (1.2–2.2)	1.7 (1.2–2.3)	1.9 (1.4–2.5)
vPS	297	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.4 (1.1–1.7)	1.3 (1.1–1.6)
SV	69	0.80 (0.53–1.2)	0.81 (0.54–1.2)	0.96 (0.63–1.5)	0.9 (0.62–1.2)
AVSD	151	1.0 (0.77–1.4)	1.0 (0.76–1.3)	1.2 (0.87–1.6)	1.1 (0.88–1.4)
Septal defects	6,001	1.0 (0.98–1.10)	1.0 (0.98–1.1)	1.1 (1.0–1.1)	1.1 (1.0–1.2)
VSD	4,032	1.1 (1.1–1.2)	1.1 (1.1–1.2)	1.1 (1.1–1.2)	1.2 (1.1–1.2)
ASD	1,969	0.89 (0.82–0.96)	0.89 (0.81–0.96)	0.95 (0.87–1.0)	1.0 (0.94–1.1)
Others	1,654	1.2 (1.2–1.3)	1.2 (1.2–1.3)	1.2 (1.2–1.3)	1.2 (1.2–1.3)

Model 0: The traditional logistic regression was employed as the crude model. Model 1: An age-adjusted model. Model 2: Building upon Model 1, additional adjustments were made to account for potential confounders, including maternal ethnicity, household income, maternal education level, season of pregnancy, active smoking, residence location, migrant status, temperature, and $PM_{2.5}$. Model 3: Essentially a refinement of Model 2, utilizing a marginal structural logistic model with inverse probability weights (IPW) based on the linear model (LM).

ALAN indicates artificial light at night; APVR, anomalous pulmonary venous return; ASD, atrial septal defect; AVSD, atrioventricular septal defects; CHD, congenital heart disease; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; IAA, interrupted aortic arch; LVOTO, left ventricular outflow tract obstruction; OR, odds ratio; PA, pulmonary atresia; PAPVC, partial anomalous pulmonary venous connection; RVOTO, right ventricular outflow tract obstruction; SV, single ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, d-transposition of the great arteries; ToF, tetralogy of Fallot; vAS, very active stenosis; vPS, valvular pulmonary stenosis; VSD, ventricular septal defect.

risk of total CHD compared with the lowest quartile with OR values of 1.0 (0.94–1.1), 1.2 (1.1–1.3), and 1.4 (1.3–1.5), respectively. The association followed a monotonic exposure–response relationship. This trend remained consistent across most disease subtypes, with observed differences as detailed in Table 4 and Table 5. Notably, a small number of subtypes, such as truncus arteriosus, very active stenosis, and partial anomalous pulmonary venous connection, did not exhibit the highest ORs in Q4; however, the *P*-values for trend were not statistically significant.

Stratified analyses

The positive association between ALAN and CHD was consistent across subpopulations. In Table 6, the offspring of mothers with lower education (OR: 1.3, 95% CI: 1.2, 1.3) showed a slightly higher risk of CHD than those of mothers with higher education levels (OR: 1.1, 95% CI: 1.0, 1.3). We estimated a stronger effect of exposure to ALAN among families with an annual income of 2,500 yuan or less (OR: 1.2, 95% CI: 1.1, 1.3) than families with an annual income above 5,000 yuan (OR: 1.1, 95% CI: 0.94, 1.2). Furthermore, we found a greater effect estimate among the usual resident mothers (OR: 1.3, 95% CI: 1.2, 1.4) than the migrants (OR: 0.94, 95% CI: 0.85, 1.0). We observed multiplicative interactions for maternal education level, household income, and migrant status. In addition, across all sociodemographic factors assessed, we observed additive interactions with ALAN and CHD risk for migrant status, maternal education level, and household income. Specifically, the RERI (95% CI) was −1.1 (−1.3, −0.94) for migrant mothers compared to usual resident mothers, −0.21 (−0.31, −0.06) for mothers with university or higher education compared to those with high school or below education, and −0.54 (−0.75, −0.32) for mothers with a household income >5,000 compared to those with a household income <2,500 (Figure 2).

TABLE 3. Association Between Maternal ALAN Exposure During Pregnancy (1-unit Increase, nW/cm²/sr) and the Risk of CHD by Severity in Offspring

CHD Phenotypes	N	Model 0 OR	Model 1 OR	Model 2 OR	Model 3 OR
Severe	619	1.4 (1.3–1.6)	1.4 (1.2–1.6)	1.5 (1.3–1.7)	1.6 (1.4–1.8)
Nonsevere	6,469	1.1 (1.0–1.1)	1.1 (1.0–1.1)	1.1 (1.0–1.2)	1.1 (1.1–1.2)

(1) Model 0: The traditional logistic regression was employed as the crude model. (2) Model 1: An age-adjusted model. (3) Model 2: Building upon Model 1, additional adjustments were made to account for potential confounders, including maternal ethnicity, household income, maternal education level, season of pregnancy, active smoking, residence location, migrant status, temperature, and $PM_{2.5}$. (4) Model 3: Essentially a refinement of Model 2, utilizing a marginal structural logistic model with inverse probability weights (IPW) based on the linear model (LM).

ALAN indicates artificial light at night; CHD, congenital heart disease; OR, odds ratio.

Sensitivity analyses

The sensitivity analyses revealed consistent results when calculating exposure to ALAN in 1000-m buffers (eFigure S4; https://links.lww.com/EDE/C250) or excluding certain participants (eTable S3 and Figure S5; https://links.lww.com/EDE/C250). Results were also robust in the presence of unmeasured confounding bias according to *E*-values displayed in eTable S4; https://links.lww.com/EDE/C250 (ranging from 1.6 to 1.7). The results also remain consistent regardless of whether the confounder data were imputed (eFigure S6; https://links.lww.com/EDE/C250).

DISCUSSION

In this large case–control study from southern China, we examined the potential impact of maternal exposure to ALAN during pregnancy on the risk of CHD and its subtypes. We also investigated the interactions between exposure to ALAN and sociodemographics. In addition to the main effect estimates, we observed dose–response relationships between the exposure and the outcomes. We also estimated a stronger effect of the exposure on the risk of severe CHD. Both multiplicative and additive interaction analyses revealed negative interactions between ALAN and specific sociodemographic factors, including migrant status, maternal education level, and household income, on CHD risk. Furthermore, we estimated that the groups with lower education levels, lower household income, and being usual residents in urban areas were more vulnerable to the adverse effects of exposure, revealing the disparities across sociodemographics. Using advanced causal inference methods and multiple sensitivity analyses, our study provides the most comprehensive set of evidence to date on the association between exposure to ALAN and CHD.

The increased risk of CHD in newborns associated with exposure to ALAN during pregnancy is biologically plausible. Potential mechanisms include maternal circadian rhythm and hormone level disruptions, as well as disturbances in fetal hormone and metabolic pathways.[48,49] However, these mechanisms need to be elucidated through future experimental studies. According to our estimates, exposure during pregnancy poses a higher risk for severe CHD compared with the nonsevere CHD. Existing research evidence on this topic is limited. However, based on the current knowledge of mechanisms and the observations in our study, we hypothesize that exposure to ALAN might induce CHD by pathways related to maternal circadian rhythm disruptions that may present a higher risk than other factors. These pathways should be given special attention and potentially blocked to reduce the risk and severity of CHD. Future research should aim to clarify the mediating pathways through which ALAN exposure affects health outcomes.

Further, we identified interaction effects from maternal education level, household income, and migrant status around the link between exposure to ALAN and CHD. Although the influence of maternal characteristics on the impact of ALAN on CHD has not been previously studied to our knowledge, our results align with studies suggesting that maternal characteristics could modify the effects of air pollutants on pregnancy outcomes.[50–52] First, offspring born to mothers with lower educational backgrounds are estimated to be more susceptible to the effects of light at night on CHD. Higher maternal education often correlates with better awareness of environmental pollutants, and healthier lifestyle choices, which could help mitigate the impact of ALAN on pregnancy outcomes. In contrast, lower educated mothers may encounter inadequate nutrition, and unhealthy behaviors like smoking,[53] which could amplify their vulnerability to environmental pollutants and adverse pregnancy outcomes. However, it is important to note that the CIs for the estimates largely overlapped across educational status groups, suggesting that these findings should be interpreted with caution. Further studies with larger sample sizes are needed to confirm these associations and explore potential underlying mechanisms. Second, lower income women are also at a higher risk of giving birth to fetuses with CHD compared to higher income women. Low-income mothers are more likely to experience limited access to medical services and difficulties in managing health risks. They may also face inadequate sanitation and restricted access to healthcare and social resources,[54] further exacerbating their risk of adverse pregnancy outcomes. Third, we estimated that the impact of ALAN exposure during pregnancy on CHD was stronger in the offspring of usual resident mothers compared with migrant mothers. This finding was inconsistent with previous findings, which generally indicated that the migrants are more vulnerable to the health effects of air pollution.[55,56] Possible reasons are socioeconomic and healthcare-seeking behavioral differences. Usual residents are more likely to utilize local healthcare institutions due to the convenience and coverage provided by local health insurance policies, regardless of their socioeconomic status (SES). This ensures a comprehensive detection of CHD cases among this population. In contrast, migrants seeking medical care in Guangdong's healthcare institutions may represent a subgroup with relatively better

TABLE 4. Association Between Maternal ALAN Exposure During Pregnancy (by Quartiles) and the Risk of CHD and Its Subtypes in Offspring

		OR				
		Q1	Q2	Q3	Q4	
CHD Phenotypes	N	n= 4562	n= 4564	n= 4563	n= 4563	*P* for Trend[a]
Total CHDs	9,764	1.0	1.0 (0.94– 1.1)	1.2 (1.1–1.3)	1.4 (1.3–1.5)	<0.01
Conotruncal defect	760	1.0	1.3 (0.97–1.6)	1.5 (1.2–1.9)	2.0 (1.6–2.5)	<0.01
Truncus arteriosus	51	1.0	1.17 (0.56–2.5)	0.97 (0.45–2.1)	0.7 (0.30–1.5)	0.09
TGA	293	1.0	1.5 (1.0–2.3)	2.1 (1.4–3.1)	2.5 (1.7–3.7)	<0.01
DORV	91	1.0	1.1 (0.52–2.3)	1.1 (0.56–2.3)	2.8 (1.5–5.1)	<0.01
TOF	325	1.0	1.1 (0.80–1.6)	1.3 (0.91–1.8)	1.9 (1.3–2.6)	<0.01
LVOTO	500	1.0	1.1 (0.67–1.7)	1.4 (0.90–2.1)	2.3 (1.5–3.4)	<0.01
IAA	233	1.0	1.1 (0.64–2.0)	1.5 (0.86–2.5)	2.5 (1.6–4.1)	<0.01
vAS	37	1.0	1.3 (0.48–3.6)	1.5 (0.59–4.0)	1.2 (0.44–3.3)	0.71
HLHS	44	1.0	1.0 (0.45–2.4)	0.37 (0.12–1.2)	1.7 (0.76–3.6)	0.27
CoA	186	1.0	1.0 (0.57–1.9)	1.7 (1.0–3.0)	2.8 (1.7–4.6)	<0.01
APVR	90	1.0	0.96 (0.46–2.0)	1.3 (0.65–2.5)	2.0 (1.1–3.6)	0.01
PAPVC	17	1.0	11.7 (2.1–64.3)	7.6 (1.3–42.5)	9.1 (1.6–50.8)	0.42
TAPVC	73	1.0	0.83 (0.39–1.8)	1.2 (0.61–2.4)	1.9 (1.0–3.5)	0.01
RVOTO	539	1.0	0.91 (0.67–1.2)	1.1 (0.85–1.5)	1.7 (1.3–2.3)	<0.01
Ebstein anomaly	24	1.0	0.11 (0.01–0.82)	0.54 (0.18–1.6)	1.2 (0.48–2.9)	0.15
TA	67	1.0	0.58 (0.10–3.5)	1.0 (0.22–4.6)	2.3 (0.63–8.5)	0.24
HRHS	53	1.0	0.98 (0.41–2.3)	1.5 (0.67–3.2)	1.8 (0.86–3.9)	0.06
PA	98	1.0	1.9 (0.93–3.7)	1.4 (0.66–2.8)	3.6 (1.9–6.6)	<0.01
vPS	297	1.0	0.87 (0.60–1.3)	1.2 (0.86–1.7)	1.6 (1.1–2.2)	<0.01
SV	69	1.0	0.63 (0.34–1.2)	0.46 (0.24–0.90)	0.81 (0.47–1.4)	0.12
AVSD	151	1.0	0.84 (0.49–1.5)	1.1 (0.69–1.9)	1.3 (0.83–2.1)	0.75
Septal defects	6,001	1.0	0.93 (0.84–1.0)	0.97 (0.88–1.1)	1.1 (1.0–1.2)	0.38
ASD	1,969	1.0	0.84 (0.73–0.97)	0.94 (0.82–1.1)	0.96 (0.84–1.1)	0.02
VSD	4,032	1.0	0.98 (0.88–1.1)	0.98 (0.88–1.1)	1.2 (1.1–1.4)	<0.01
Others	1,654	1.0	1.1 (0.97–1.2)	1.2 (1.1–1.3)	1.4 (1.3–1.5)	<0.01

Effects were evaluated employing a causal inference model with adjusting for maternal ethnicity, household income, maternal education level, season of pregnancy, active smoking, residence location, migrant status, temperature, and $PM_{2.5}$.

[a]*P* for trend corresponded to the marginal structural logistic models comparing quartiles (Q1 as the reference) of ALAN.

ALAN indicates artificial light at night; APVR, anomalous pulmonary venous return; ASD, atrial septal defect; AVSD, atrioventricular septal defects; CHD, congenital heart disease; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; IAA, interrupted aortic arch; LVOTO, left ventricular outflow tract obstruction; OR, odds ratio; PA, pulmonary atresia; PAPVC, partial anomalous pulmonary venous connection; RVOTO, right ventricular outflow tract obstruction; SV, single ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, d-transposition of the great arteries; ToF, tetralogy of Fallot; vAS, very active stenosis; vPS, valvular pulmonary stenosis; VSD, ventricular septal defect.

TABLE 5. Association Between Maternal ALAN Exposure During Pregnancy (by Quartiles) and the Risk of CHD by Severity in Offspring

		OR				
CHD Phenotypes	N	Q1	Q2	Q3	Q4	*P* for Trend[a]
N		4,562	4,564	4,563	4,563	
Severe	619	1.0	1.2 (0.90–1.6)	1.3 (1.0–1.8)	2.1 (1.7–2.7)	<0.01
Nonsevere	6,469	1.0	0.95 (0.87–1.1)	0.99 (0.90–1.1)	1.2 (1.1–1.3)	0.05

Effects were evaluated employing a causal inference model with adjusting for maternal ethnicity, household income, maternal education level, season of pregnancy, active smoking, residence location, migrant status, temperature, and $PM_{2.5}$.

[a]*P* for trend corresponded to the marginal structural logistic models comparing quartiles (Q1 as the reference) of ALAN.

ALAN indicates artificial light at night; CHD, congenital heart disease; OR, odds ratio.

economic conditions and higher SES, while those with lower SES might be more inclined to seek care at facilities outside the surveillance system.

This study has some notable strengths. First, it is the first investigation to our knowledge into the relationship between maternal exposure to ALAN and CHD and

TABLE 6. Stratified Analyses for Maternal ALAN Exposure During Pregnancy and CHD in Offspring

Stratified Variable	CHDs/Number of Observations	OR	*P* for Interaction
Maternal education level			
High school or below	7,512/13,895	1.3 (1.2–1.3)	<0.01
University or higher	2,252/4,357	1.1 (1.0–1.3)	
Residence location			
Urban	6,336/11,800	1.2 (1.2–1.3)	0.42
Rural	3,428/6,452	1.2 (1.1–1.3)	
Maternal age			
<35	8,342/15,998	1.2 (1.2–1.3)	0.72
≥35	1,422/2,254	1.3 (1.1–1.4)	
Household income			
≤2500	3,655/7,056	1.2 (1.1–1.3)	0.02
2501–5000	4,248/8,034	1.3 (1.2–1.4)	
>5000	1,861/3,162	1.1 (0.94–1.2)	
Migrant status			
Migrant	2,102/3,820	0.94 (0.85–1.0)	<0.01
Usual resident	7,662/14,432	1.3 (1.2–1.4)	

Effects were evaluated employing a causal inference model with adjusting for maternal ethnicity, household income, maternal education level, season of pregnancy, active smoking, residence location, migrant status, temperature, and $PM_{2.5}$.

ALAN indicates artificial light at night; CHD, congenital heart disease; OR, odds ratio.

its specific subtypes in offspring, employing advanced causal inference methods. We also explored and considered interaction effects from sociodemographic characteristics, providing a comprehensive examination of the multifaceted relationship between light-at-night exposure and CHD. Second, we used individual data derived from a CHD registry, featuring a large sample size for this rare outcome, ensuring sufficient statistical power. Additionally, the clinical confirmation criteria for heart defects were standardized, and a panel of clinical physician experts rigorously reviewed the medical records, maximizing the accuracy of case classification.

However, there may be some limitations to our study. First, case–control studies generally have limitations in determining the temporal order between exposure and outcomes, thus, we are not able to provide clear causal clues although the ALAN exposure data we collected should theoretically occur before the outcome. Second, in this study, the number of cases exceeded the number of controls. While the parents of the CHD cases generally were willing to participate in scientific research, the parents of some healthy children were not willing to do so, resulting in a lower participation rate among the controls. In addition, the staff in some centers did not promptly collect matched controls for the cases they recruited, resulting in slower sampling. Consequently, while the response rate for the case group was almost 100%, the response rate for the control group was slightly lower and varying across centers. This missing control issue may result in selection bias and a reduced statistical power. The issue was also reported in multiple previous studies of CHD. The same dataset has been used in our previous studies.[57,58] Third, in our study, we assessed maternal ALAN exposure during pregnancy using geocoded residential addresses and measured in years, which may introduce exposure misclassification as participants pregnant in the same year and living

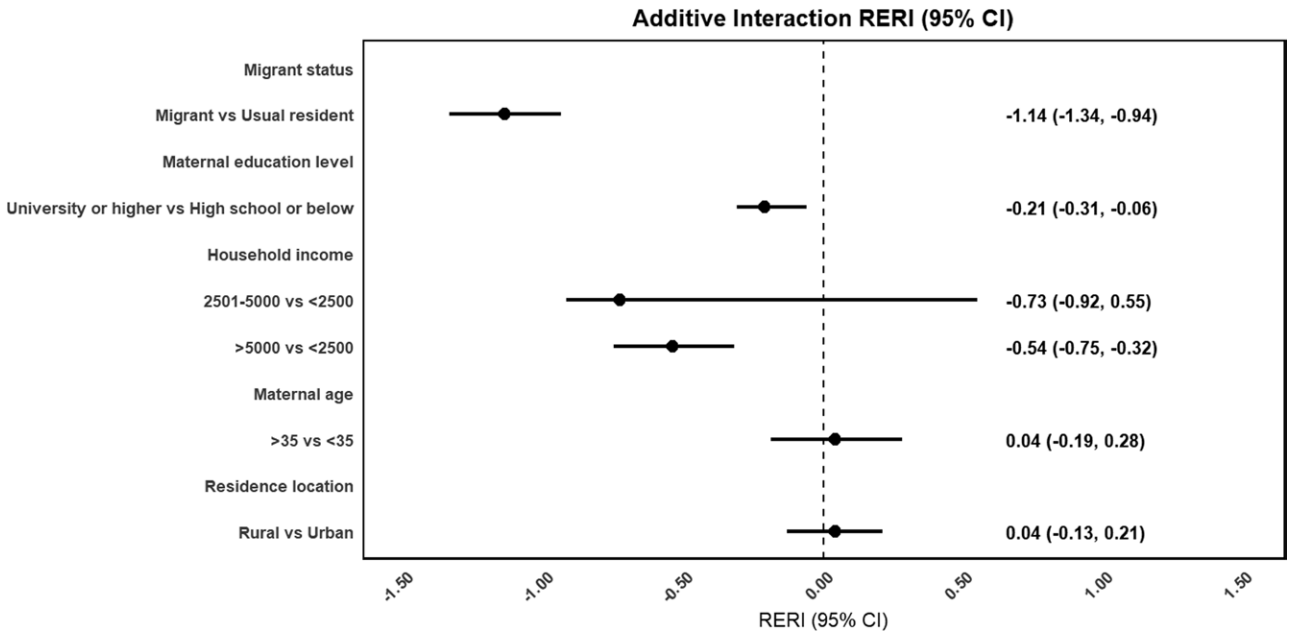

FIGURE 2. Estimate for additive interaction between ALAN and sociodemographic factors. ALAN indicates artificial light at night; CI, confidence interval; OR, odds ratio; RERI, relative excess risk due to interaction.

close to each other may be assigned similar exposure values. However, this misclassification is likely to be Berkson and classical errors, potentially biasing the effect estimates toward the null.[59] Additionally, the high-resolution data on light at night we used can alleviate the misclassification issue to some extent and the use of yearly data is appropriate as the variation of ALAN within a year is generally limited. Fourth, although the GRCHD is a population-based surveillance system, not all CHD cases in the province are captured, which may introduce some degree of selection bias. However, the registry strategically includes institutions from various geographic areas, prioritizing facilities with the capacity to accurately diagnose and report CHD cases. Importantly, the CHD prevalence recorded in the GRCHD closely aligns with national estimates for China,[60] reinforcing its representativeness. Additionally, assessments conducted by the registry authorities indicate no significant differences in sociodemographic characteristics between births occurring within and outside the GRCHD-covered hospitals.[61] This suggests that any potential selection bias is unlikely to substantially impact our findings. Finally, while we adjusted for several key confounders, unmeasured factors such as genetic susceptibility and other environmental exposures may also contribute to disease risk. For instance, genetic factors have been implicated in CHD, with studies suggesting that rare damaging recessive genotypes contribute to at least 2.2% of cases.[62] However, there is limited evidence to infer the OR or RR of CHD associated with the presence or absence of these genotypes, making it challenging to directly compare them with our *E*-value. In addition to the factors we adjusted for (i.e., $PM_{2.5}$ and temperature), other environmental factors such as SO_2 and NO_2 may also act as potential confounders. A previous study indicated that the effect estimates of these factors on CHD risk ranged from 1.03 to 1.53.[63] These effect estimates fall below our *E*-value, suggesting that these unmeasured confounders are unlikely to overturn our findings. However, as with other observational studies, we cannot entirely rule out the possibility of unmeasured confounding, nor can we guarantee that the estimated effects of all unmeasured confounders on CHD risk are below 1.7 (our *E*-value). Nevertheless, an OR of 1.7 represents a relatively large effect size, indicating that our conclusions are, to some extent, relatively robust against unmeasured confounding.

CONCLUSION

We observed that maternal exposure to ALAN during pregnancy was linked to an increased risk of CHD in offspring. We observed this association across nearly all CHD subtypes, especially in severe CHD. While our findings estimate that lower education, lower income, and usual resident status may contribute to an increased susceptibility to ALAN exposure, the imprecision of interaction estimates for education status warrants cautious interpretation. Further well-designed cohort studies are needed to validate these associations and explore potential underlying mechanisms.

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