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Does maternal environmental tobacco smoke interact with social-demographics and environmental factors on congenital heart defects?☆

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ABSTRACT

Congenital heart defects (CHDs) are a major cause of death in infancy and childhood. Major risk factors for most CHDs, particularly those resulting from the combination of environmental exposures with social determinants and behaviors, are still unknown. This study evaluated the main effect of maternal environmental tobacco smoke (ETS), and its interaction with social-demographics and environmental factors on CHDs in China. A population-based, matched case-control study of 9452 live-born infants and stillborn fetuses was conducted using the Guangdong Registry of Congenital Heart Disease data (2004–2014). The CHDs were evaluated by obstetrician, pediatrician, or cardiologist, and confirmed by cardia tomography/catheterization. Controls were randomly chosen from singleton newborns without any malformation, born in the same hospital as the cases and 1:1 matched by infant sex, time of conception, and parental residence (same city and town to ensure sufficient geographical distribution for analyses). Face-to-face interviews were conducted to collect information on demographics, behavior patterns, maternal disease/medication, and environmental exposures. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals of ETS exposure on CHDs while controlling for all risk factors. Interactive effects were evaluated using a multivariate delta method for maternal demographics, behavior, and environmental exposures on the ETS-CHD relationship. Mothers exposed to ETS during the first trimester of pregnancy were more likely to have infants with CHD than mothers who did not (aOR = 1.44, 95% CI 1.25–1.66). We also observed a significant dose-response relationship when mothers were exposed to ETS and an increasing number of risk factors and CHDs. There were greater than additive interactions for maternal ETS and migrant status, low household income and paternal alcohol consumption on CHDs. Maternal low education also modified the ETS-CHD association on the

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multiplicative scale. These findings may help to identify high-risk populations for CHD, providing an opportunity for targeted preventive interventions.

1. Introduction

Congenital heart defects (CHDs) are among the most common birth defects and remain a major cause of death in infancy and childhood (Marelli et al., 2007; Hoffman et al., 2004). The etiology of most congenital heart anomalies is uncertain. Many previous studies have indicated that 70%–85% are caused by a complex interaction between environmental teratogens and genetic factors (Botto and Correa, 2003; Wilson et al., 1998), but knowledge regarding the joint effects of environmental factors and other CHD risk factors, and their interactions on CHDs, are still limited (Oyen et al., 2009; Jenkins et al., 2007).

It is reported that active maternal smoking during pregnancy has been associated with increased odds of CHDs (Malik et al., 2008; Alverson et al., 2011). However, active smoking among mothers in China is quite rare, while smoking prevalence among men is high. Exposure to environmental tobacco smoke (ETS) among women in China is estimated to range from 68% to 71.6 (Xiao et al., 2010).

Studies examining ETS and CHD, especially the potential interaction between ETS and other CHD risk factors, are limited. Further, some non-inherited, potentially modifiable, factors, such as parental diet and alcohol consumption and environmental factors may alter the ETS association with CHD (Jenkins et al., 2007). Prior studies reported that low socio-economic status (SES) is associated with CHD (Carmichael et al., 2003; Agha et al., 2011; Yu et al., 2014).

While the biological plausibility of interactive relationships with SES and social factors with ETS on CHDs are not clear, it has been reported that economically disadvantaged individuals may be more likely to have greater exposure to adverse risk factors (e.g. smoke more cigarettes), and that this accumulation of risk factors may increase the risk of CHDs compared with those in high SES groups (Rauh et al., 2004; Townsend et al., 1991; Bobak, 2000; Heslop et al., 2001). In addition, active smoking among pregnant women has been associated with lower intake of micronutrients, lower quality diet and high fat diet (Margetts and Jackson, 1993; Rogers et al., 1998; Thornton et al., 1994). Meanwhile, populations with low SES also tend to have lower-quality diets and inadequate intake of trace elements, especially for iron, folic acid, and micronutrients, which are essential for organ generation (Block and Abrams, 1993; Simon et al., 1992).

Understanding the relationship between ETS, socio-economic status, maternal environmental exposures and their joint effects on CHD is important for developing interventions to prevent CHDs. To fill this gap in knowledge, this study evaluated whether maternal ETS exposure is associated with an increased risk of CHD, and if this EHS-CHD association is modified by the presence of maternal sociodemographic, environmental exposures and/or other and parental behaviors.

2. Material and methods

2.1. Study design and population

This is a population-based, matched case-control study of live-born infants and stillborn fetuses diagnosed with CHDs from 2004 to 2014. Cases were identified from the Guangdong Registry of Congenital Heart Disease (GRCHD), an ongoing population-based CHD surveillance system in Southern China (Ou et al., 2016).

The CHD defects were defined using a modified code from the International Classification of Diseases (ICD-10: Q20.000-Q28.000). All newborns were evaluated by an obstetrician, pediatrician, or pediatric cardiologist before discharge, or within 72 h after birth. All echocardiograms of CHD cases were reviewed by two specialty trained echocardiologists. When necessary, some CHDs were confirmed by computed tomography, cardiac catheterization, surgery, or autopsy. Controls were randomly chosen singleton newborns without any malformation, born in the same hospital (with similar diagnosis criteria and practice) as the cases and 1:1 matched by infant sex, time of conception and parents' residence (same city and same town, with similar sociodemographic profile as the cases).

Inclusion criteria: Mothers of all CHD and non-CHD infants who had been living in the monitored district for $\geq$ 6 months were eligible to participate in this study. To minimize recall bias of exposure by mothers, all cases and controls were recruited when they were <1 year old (ranging: 17 gestational weeks~ 1 year old). The cases in the final analysis included isolated CHD live-born infants and stillborn fetuses defined as congenital structural defects in the cardiovascular system without any extra-cardiac anomalies. All CHD were further classified into nine cardiac subtypes Botto et al., 2007; Øyen et al., 2009 (Table 1) using *ICD-10CA* codes.

Exclusion criteria: 1) Cases with syndromes caused by gene mutations or chromosomal aberrations; 2) Non-singleton cases; 3) Family history of heart defects; 4) Preterm infants (<38 weeks gestation) with only PDA (Preterm infants tend to have more PDA); 5) Baby age>=1; and 6) non-isolated CHD with extra-cardiac defects.

The program was approved by the Ethics Committee of Guangdong General Hospital. Informed Consent was obtained from the parents of the study subjects. All investigations were performed in accordance with the institutional guidelines.

2.2. Data collection and ETS definition

All infants with CHD are reported, by mandate, to the national registry and GRCHD by obstetricians, ultrasound physicians and pediatricians. All clinical information (structural heart defects, chromosomal abnormalities, and syndromes) was abstracted from medical records. Face-to-face interviews were conducted during the mother's stay in inpatient or outpatient departments when the babies were younger than 1 year. A pregnancy calendar was used in combination with a multilevel structured questionnaire to assist mothers in recalling the major milestones of pregnancy and timing of exposure throughout pregnancy. Additionally, mothers of control infants were interviewed after his/her matched case, and any difference in the time of conception between the case and matched control was restricted to no more than 3 months. Maternal and paternal information collected included: demographical information (ethnicity, age, residential location, migrant status (moving from rural areas to Guangdong areas for work without permanent city residence), household income, education level), reproductive history (parity, gravidity, abnormal reproductive history), occupational and environmental exposures prior to or during pregnancy,