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Early-life indoor environmental exposures increase the risk of childhood asthma

Yang-Ching Chen[a,b,1], Ching-Hui Tsai[a,1], Yungling Leo Lee[a,c,*]

[a] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17 Xuzhou Road, Zhongzheng District, Taipei 100, Taiwan
[b] Department of Family Medicine, Taipei City Hospital, ZhongXing Branch, 10341, No. 145 Zhengzhou Rd., Datong Dist., Taipei 103, Taiwan
[c] Research Center for Genes, Environment and Human Health, College of Public Health, National Taiwan University, Taipei, Taiwan

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ABSTRACT

We aim to explore the relationships between exposure to dampness, pets, and environmental tobacco smoke (ETS) early in life and asthma in Taiwanese children, and to discuss their links to early- and late-onset asthma. We conducted a 1:2 matched case-control study from the Taiwan Children Health Study, which was a nationwide study that recruited 12-to-14 year-old school children in 14 communities. The 579 mothers of the participants were interviewed by telephone about their children's environmental exposures before they were 5 years old, including the *in-utero* period. Childhood asthma was associated with exposure to early life environmental factors, such as cockroaches (OR = 2.16; 95% CI, 1.15–4.07), visible mould (OR = 1.75; 95% CI, 1.15–2.67), mildewy odors (OR = 5.04; 95% CI, 2.42–10.50), carpet (OR = 2.36; 95% CI, 1.38–4.05), pets (OR = 2.11; 95% CI, 1.20–3.72), and more than one hour of ETS per day (OR = 1.93; 95% CI, 1.16–3.23). The ORs for mildewy odors, feather pillows, and ETS during early childhood were greater among children with late-onset asthma. Cockroaches, carpet, pets, and *in-utero* exposures to ETS affected the timing of early-onset asthma. Exposure to these factors led to dose-responsiveness in the risk of asthma. And the earlier exposures may trigger the earlier onset. Interventions in avoiding these environmental exposures are necessary for early-prevention of childhood asthma.

Introduction

Asthma is a disease that involves complicated interactions during genetic, prenatal, and postnatal environments. Both *in-utero* exposure and early-life factors play important roles in the development of asthma (Kumar, 2008). Because novel immune maturation events occur from pregnancy until 2 years after birth, early life environmental exposures represent critical window of immune sensitivty (Dietert and Zelikoff, 2008). Researchers suggested that even transient environmental exposures might influence the developing immune system (Milner and Gergen, 2005). Early life risk factors reported to date include environmental chemicals and toxicants (e.g., tobacco smoke, paracetamol), dietary intake (e.g., vitamins and fatty acids), maternal stress, and respiratory tract infections (e.g., virus infection). No single risk factors appear to hold the answers of the development of childhood asthma (Holt and Sly, 2007). These environmental factors may act together to impair the immune system, increase apoptosis of Th1 cell and lead to a Th2 skewed immune response (Akkoc et al., 2008), which later presents with wheezing or asthma. The preschool children spend a considerable of time in their homes, therefore, the indoor environment provides the initial and important exposures for those young children (Lupoli et al., 2009). There are many exposures found in the indoor proven to be associated with asthma, including house dust, dander from animals, mould, cockroaches (Zeldin et al., 2006), cooking fumes (Dodge, 1982), and environmental tobacco smoke (ETS) (Cheraghi and Salvi, 2009).

Exposure early in life to dampness, cockroaches, pets, and ETS reportedly predispose patients to asthma (Zeldin et al., 2006). Moisture damage and mould in the home increase the risk of early wheezing (Belanger et al., 2003; Karvonen et al., 2009). Sensitization to cockroaches has been suggested to correlate with lower pulmonary function and asthma prevalence among school children in Taiwan (Lee et al., 2003; Lin et al., 2002). A correlation between exposure early in life to pets and atopy disease, however, remains unclear due to inconsistent results seen in previous studies (Jaakkola et al., 2002a; Nafstad et al., 2001). Certainly, maternal smoking and ETS are well-known risks for childhood asthma (Jindal and Gupta, 2004; Li et al., 2005). Recent studies have found that exposure ETS *in-utero* is even more harmful than postnatal exposure (Gilliland et al., 2003; Horak et al., 2007; Jaakkola et al., 2006). Respiratory tract development occurs antenatally and exposure to environmental factors during the critical period of

Abbreviations: ETS, environmental tobacco smoke; OR, odds ratio; CI, confidence interval.

* Corresponding author at: Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17 Xuzhou Road, Zhongzheng District, Taipei 100, Taiwan. Tel.: +886 2 33668016; fax: +886 2 23920456.
E-mail address: leolee@ntu.edu.tw (Y.L. Lee).

[1] Y.-C. Chen and C.-H. Tsai contributed equally to this article.

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organogenesis might exert potent long term effects. Harmful environmental exposures might permanently alters the structure of the lung, such as smooth muscle, elastic recoil properties, epithelial organization and immune function (Cook et al., 1998). The earlier life environmental allergen exposures might determine the earlier timing of asthma incidence. According to several previous studies, environmental exposure in early life may produce an early onset of persistent asthma symptoms (Kurukulaaratchy et al., 2004). Early-life factors such as recurrent respiratory infections, low social class at birth and parental smoking associated independently with early-onset, but not late-onset persistent wheeze development. A rodents study showed that *in utero* exposure to ETS have increased bronchial reactivity (Joad et al., 1999).

In this study, we explore in detail the relationships between early-in-life exposure to environmental exposures and asthma in Taiwanese children, and discuss their links to early- or late-onset asthma in children. Hence, the objectives for the present study were to test (1) whether exposure in the environment to these factors elevate the risk of childhood asthma, and (2) the dose-responsiveness of such exposure. Furthermore, we would also like to understand the difference between the effects on early-onset and late-onset asthma. We designed a case-control study using data from our previous Taiwan Children Health Study (TCHS) cohort.

Material and methods

Subject selection

We began the present case-control study by using the Taiwan Children Health Study (TCHS) population. Details of the TCHS have already been described (Tsai et al., 2010). Briefly, the TCHS was a nationwide population-based study that recruited 5804 seventh and eighth grade children, of ages 12-to-14, from the public schools of 14 Taiwanese communities in 2007. A parent of each child provided written informed consent and completed a self-administered questionnaire. Data from the TCHS was considered baseline data for the present study.

A matched sampling design was used to select participants for this nested case-control study. Our study consisted of 4982 of the 5804 children, who were non-smoking children aged 12–14 years old at the time of enrollment in the TCHS. Of these 4982 children, we selected those with doctor-diagnosed asthma ($n = 287$). Asthma cases and asthma- and wheeze-free controls were matched on age, sex, and same community. Based on 3 kinds of ages, 2 genders, and 14 communities, we then divided asthma- and wheeze-free children into 84 age-, sex-, and community-specific strata. Controls were randomly selected on a 1:2 basis according to the number of cases in each stratum. In a structured telephone interview, the biological mothers of the participants were asked to provide details about their children, including demographics, family history of atopic diseases, aspects of the indoor environment during pregnancy, and postnatal exposures at home before the participant was 5 years old (i.e. to ETS, pets, cockroaches, carpet use, and dampness). Children unaccompanied by their biological mothers were excluded from our study population. Three well-trained field workers performed the telephone interviews by using standardized interview skills. The study protocol was approved by the Institutional Review Board at National Taiwan University Hospital Research Ethics Committee (number: 200902042R), and complied with the principles outlined in the Helsinki Declaration (Hopper et al., 1995).

Exposure assessment

Environment tobacco smoke status during maternal pregnancy was determined by approaching detailed exposure frequency and doses such as the number of family members who smoked, the numbers and hours of cigarettes the mother was exposed to each day, and the smoking statuses of both the biological father and mother. Similar questions about ETS exposure were repeatedly asked about when the participants were younger than 5 years old.

For postnatal residential exposure for the participant before 5 years old, we also gathered information about feather pillows, carpet use, pets, the presence of cockroaches, and dampness (including water damage, visible mould, and mildewy odors as well as the use of dehumidifiers, air conditioners, and air cleaners). We further inquired about the frequency of such exposure. For participants who were exposed to feather pillows and pets (including dogs, cats, birds, mice, and rabbits), we inquired whether the exposure was for less than 3 years or 3–5 years.

Case definition

We distinguished asthma cases and controls by asking two questions at the end of interview: "Has your child ever experienced difficulty breathing, or have you observed any wheezing or whistling from their chest?" and "Has a doctor ever diagnosed your child as having asthma?" If the answers were "Yes" to both questions, we considered this an asthma case. If the answers were "No" to both questions, we considered this a control case. If the answers differed from each other, we excluded this data to avoid information bias. Once the asthma cases had been confirmed, we further asked about the age when the doctor diagnosed the child as having asthma. We classified the age of onset as early-onset (5 years old and below) and late-onset (after 5 years old), considering the exposure assessment was at the time period before 5 years old.

Statistical analysis

For our matched case-control study design, we used conditional logistic regression to assess the risk of childhood asthma for each individual type of exposure. Odds ratios (OR) and 95% confidence intervals represented the effects of each early-life exposure on developing childhood asthma. For those with significant exposure, we further analyzed the different types of asthma by defining the asthma as early-onset and late-onset. The OR for the association of such exposures with early-onset and late-onset asthma were computed using the conditional likelihood method for multinomial logistic regression models. The missing information among these participants was also included in the model by using missing indicators. For the selection of possible confounders, we included a covariate if the estimate effects changed by at least 10%. In addition, we selected some *a priori* confounders based on previous research. All of the models were adjusted for the parents' level of education (Al-Kubaisy et al., 2005; Gehring et al., 2006; Jaakkola et al., 1994), family income (Greek et al., 2006), family history of asthma (Burke et al., 2003; London et al., 2001), family history of atopy (Amdekar, 2001), and *in-utero* exposure to maternal smoking (DiFranza et al., 2004; Kumar, 2008). All tests were 2-sided at a 5% significance level and our study participant number was sufficient to reach 80% power. We used SAS version 9.1 (SAS Institute, Cary, NC, USA) software for our statistical analysis.

Results

Demographic characteristics for all the cases and controls are described in Table 1. Ultimately, 579 mothers (193 cases and 386 controls) were recruited. Of the 193 asthma cases, 131 (67.9%) were defined as early-onset and 62 (32.1%) were defined as late-onset asthma. 67.2% of the biological mothers of the 287 asthma cases received our telephone interview. As we compared the percentages of cases and controls for each characteristic (Table 1), we found