Association of Exposure to Hydrocarbons Air Pollution with Incidence of Atopic Dermatitis in Children

Chieh Wang  
Department of Chinese Medicine, China Medical University Hospital

Jeng-Dau Tsai  
Chung Shan Medical University Hospital

Lei Wan  
China Medical University

Cheng-Li Lin  
China Medical University Hospital

Chang-Ching Wei ( weilonger@gmail.com)  
Children's Hospital, China Medical University Hospital; School of Medicine, China Medical University  
https://orcid.org/0000-0003-4835-3246

Research

Keywords: atopic dermatitis, environmental pollutants, methane, air pollution, children, cohort study, hydrocarbons, non-methane hydrocarbon, total hydrocarbon

DOI: https://doi.org/10.21203/rs.3.rs-93979/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background:

There is growing evidence that air pollution may act as an important environmental risk factor in the development and aggravation of childhood atopic dermatitis (AD).

Methods:

We collected data from the Taiwan National Health Insurance research database and linked the data to the Taiwan Air Quality-Monitoring Database. Children younger than 18 years old between January 1st, 2000 and until the diagnosis of AD was made, or December 31st, 2012, were selected from the database. We measured the incidence rate and hazard ratios for AD, and stratified by quartiles (Q1-Q4) of air pollutant concentration. Multivariable Cox proportional hazards models were also applied by adjusting for age, sex, monthly income, and level of urbanization.

Results:

Compared with those exposed to the concentrations in the Q1 quartile, the adjusted hazard ratio (HR) for AD increased, and total hydrocarbon (THC), non-methane hydrocarbon (NMHC), and methane (CH$_4$) exposure concentrations ranged from 1.65 to 10.6, from 1.14 to 2.47, and from 1.70 to 11.9, respectively. Patients exposed to higher levels of THC, NMHC, and CH$_4$ had greater accumulative incidence rates of childhood AD.

Conclusions:

The current study demonstrated that exposure to higher concentrations of THC, NMHC, and CH$_4$ were associated with an increased risk of childhood AD.

Introduction

AD is a common chronic relapsing inflammatory skin disease associated with intense itching and recurrent eczematous lesions [1] . In a process referred to as the “atopic march”, AD is usually an early sign of other subsequent allergic disorders [2]. Up to 80% of children with AD, particularly those with early sensitization and severe disease, will eventually develop allergic rhinitis or asthma later in childhood [3]. AD most commonly begins in early childhood. Approximately 15% – 30% of children are affected worldwide, and approximately 85% of all cases begin before five years of age [4]. It often persists into or begins in adulthood, influencing about 10% of adults [5]. AD obviously influences patients’ quality of life and creates financial implications. Itching and scratching are the two main symptoms that affect the quality of life (QoL) in childhood AD, impacting on the quality of sleep, and requiring a treatment regime, affecting the ability to do sporting activities, and social embarrassment [6]. The 2006 US report from the American Academy of Dermatology, the most comprehensive contemporary research on the economic impact of AD, reveals that the total annual burden of AD was $4.228 billion. AD was the fifth-highest overall cost among all the skin diseases in the US, placing a tremendous financial burden on society [7]. Hence, it is critical to identify and control risk factors in susceptible subjects for successful treatment and prevention of childhood AD.
Over the past 30 years, the prevalence of AD has increased considerably worldwide, particularly in industrialized countries [4]. Although both genetic and environmental factors are involved in the etiology of AD, the recent increase in the prevalence of AD is mainly attributed to environmental factors [8]. There is growing evidence that air pollution may act as an important environmental risk factor in the development and aggravation of childhood AD [9-12]. A variety of air pollutants, such as particulate matter (PM), nitrogen oxide compound (NOx), environmental tobacco smoke (ETS), traffic-related air pollution (TRAP, including PM, NO, NO2, SO2, CO, CO2, O3, etc.) as well as volatile organic compounds (VOCs), have been mentioned in recent cross-sectional and birth cohort studies [8][9]. Based on the pathogenesis of AD, including skin barrier defects and immunologic dysregulation, these air pollutants probably evaporate from the surface of the skin and bind to the stratum corneum, leading to alterations in the skin microbiome, stratum corneum pH, and trans epidermal water loss (TEWL). The compounds may also tend to penetrate into the epidermis, induce oxidative stress, and activate aryl hydrocarbon receptor (AhR), which induces an inflammatory cascade in the skin [4, 13, 14]. For example, TRAP, especially ozone (O3), has been observed to alter the resident skin flora and cause predisposition to S. aureus colonization [15]. Other dust particles and diesel exhaust particulates have also been demonstrated to exert toxicological effects on human skin [16].

Although several studies support the development or aggravation of childhood AD with air pollutants, currently available evidence on skin aspects of air pollution remains relatively scarce in contrast to airway diseases such as asthma [17]. There are still limitations in previous studies, including inaccurate study design and assessment, and the presence of confounding variables (e.g., obesity, genetics, and comorbidities). For instance, several studies have considered mixtures of substances such as environmental tobacco smoke, VOCs, and NOx, which may lead to a combined impact on human health. There was also selection bias by potential misclassification in some cross-sectional studies because the diagnosis of AD was based simply on reports from the patients or their parents and was not confirmed by a physician [8].

In this study, we focused on the association between hydrocarbons and the development of childhood AD. THC, which are organic chemical compounds consisting of NMHCs and CH4, are responsible for approximately 85% of global energy consumption due to rapid industrialization and urbanization. Whether the air pollutants released during the combustion of hydrocarbons, particularly CH4, affect the body’s largest organ, the skin, remains to be discussed. Hence, to evaluate the effect of exposure to these air pollutants on the risk of AD in children, we conducted this nationwide and retrospective study from real-world data in Taiwan.

Methods And Materials

Data Source

We conducted a retrospective cohort study using the Children File, a representative database including data from half of all children randomly selected from the year 2000 registry of beneficiaries of the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD was established in 1995 and covers more than 99% of the total population in Taiwan (http://www.nhi.gov.tw/english/index.aspx). It contains all medical records, including de-identified demographic information e.g., sex, birth dates, occupation, and place of residence, and clinical information e.g., diagnostic codes based on the International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM], health management, and treatment. Because all the research data were
anonymized and encrypted to protect the individual's privacy, consent was exempted in this study. Our study was approved by the Institute Review Board of China Medical University Hospital (CRREC-103-048) in accordance with the Helsinki Declaration.

**Study Population, Outcome of Interest, End-Points, and Confounding Factors**

In this study, we obtained data from children younger than 18 years, between 1 January 2000 to 31 December, 2012. Candidates with missing data or who had been diagnosed with AD before the baseline, were excluded. Because of the chronic and relapsing characteristics of AD, AD was defined as at least 3 records of ICD-9-CM codes 691 or 691.8 made by dermatologists or pediatrics in any diagnosis field during the inpatient or ambulatory claim process, as our outcome of interest. All participants were followed from the baseline until the diagnosis of AD was made, withdrawal from the NHI, or December 31, 2012. In this study, the mean standard deviation (SD) follow-up years in patients with AD was 6.5 (3.39). The confounding factors were age, sex, residing level of urbanization, and monthly income. The level of urbanization was defined based on population density and was graded into four levels. The highest degree of urbanization was level 1, and the lowest was level 4. Monthly income was also classified into 4 groups: < NT$14,400, NT$14,400–18,300, NT$18,301–21,000, and ≥ NT$21,000.

**Exposure Measurement**

The Taiwan Air Quality Monitoring Network (TAQMN) (http://taqm.epa.gov.tw/taqm/en/PsiMap.aspx) was established by the Taiwan Environmental Protection Administration (TEPA) in 1993 (http://www.epa.gov.tw/). It comprises 74 monitoring stations around the island. The monitoring stations are fully automated and record daily readings of THC, NMHC, and CH$_4$ by ultraviolet fluorescence. Air pollution data were extracted from all monitoring stations and averaged on each day. The databases of these air pollutants were obtained from the Taiwan Air Quality-Monitoring Database (TAQMD), released by the TEPA. We linked the NHIRD and TAQMD according to the residential areas of candidates and the location of air quality-monitoring stations. A residential area was defined based on the location of the clinic and hospital that treated acute upper respiratory tract infections (ICD-9-CM code 460). The average daily concentrations of air pollutants were calculated by dividing the cumulative daily air pollutant concentration by the duration from 2000 to the endpoint for each candidate. Air pollutant concentrations were categorized into four groups based on quartiles, Q1, Q2, Q3, and Q4. THC was categorized as Q1 (<2.29 ppm), Q2 (2.29-2.40 ppm), Q3 (2.40-2.60 ppm), and Q4 (>2.60 ppm). NMHC was categorized as Q1 (<0.27 ppm), Q2 (0.27-0.35 ppm), Q3 (0.35-0.51 ppm), and Q4 (>0.51 ppm). CH$_4$ was categorized as Q1 (<2.01 ppm), Q2 (2.01-2.06 ppm), Q3 (2.06-2.11 ppm), and Q4 (>2.11 ppm).

**Statistical Analysis**

The demographic data in our study included age, sex, monthly income, level of residential urbanization, and daily average of exposure to air pollutants. The chi-squared test was used to test the distributed difference among daily average concentrations for each air pollutant by quartile and urbanization. The incidence rate of
AD (per 1000 person-years) was counted at four different air pollutant concentration levels. Cox proportional hazard regression models were applied to estimate the hazard ratios and 95% confidence intervals (CIs) for AD in Q2–Q4 levels of air pollutant concentrations compared to the Q1 level. The multivariable model was adjusted for age, sex, monthly income, and urbanization level. We also conducted the Kaplan–Meier method to estimate the cumulative incidence of AD during the follow-up, and the log-rank test was used to test the difference among air pollutant concentration levels. All the data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC) and the Statistical Package for the Social Sciences (Version 15.1; SPSS Inc., Chicago, IL). The significance level was set at p < 0.05 in all statistical tests.

Results

A total of 7304 children (2.96%) were diagnosed with AD within the cohort of 246,844 children (Between January 1, 2001 and December 31, 2012). The demographic data of the participants are shown in Table 1. The mean age (SD) of participants was 6.50 years (3.39). The proportion of boys and girls was similar (51.6% vs. 48.4%). Most participants were from the lowest monthly income family (83.4%) and resided in the most highly urbanized areas (33.2%).

In our study, we collected the data of participants under conditions of THC, NMHC, and CH₄ exposure based on the location of the Taiwan Air Quality Monitoring Station. Four concentrations of each air pollutant were categorized by quartiles, ranging from Q1 (the lowest concentration) to Q4 (the highest concentration). Tables 2-4 show the baseline characteristics of candidates exposed to 4 levels of concentrations of THC, NMHC, and CH₄. Children with the highest exposure concentrations of THC, NMHC, and CH₄ lived in areas with higher urbanization.

The incidence rate for AD increased with THC, NMHC, and CH₄ exposure concentration, increasing from 0.69 to 6.45, from 1.72 to 4.37, and from 0.73 to 7.74 per 1000 person-years, respectively. In the multivariable Cox proportional hazard regression, the adjusted HR for AD increased with the THC, NMHC, and CH₄ exposure concentrations from 1.65 to 10.6, 1.14, 2.47, and 1.70, 11.9, respectively, compared with those exposed to the corresponding concentrations in Q1 level (1.00) (Table 5).

The Kaplan-Meier plots in Fig 1 demonstrate the accumulative incidence of AD in participants exposed to 4 levels of THC, NMHC, and CH₄ concentrations, respectively. Patients exposed to higher levels of THC, NMHC, and CH₄ had a greater accumulative incidence rate of AD.

Discussion

In this population-based longitudinal study, we demonstrated that Taiwanese children exposed to higher concentrations of THC, NMHC, and CH₄ were at increased risk of developing AD, regardless of adjustment for potential confounding factors such as age, sex, monthly income, and urbanization level. Our cohort study also revealed a clear dose-response relationship between air pollution and AD. Overall, the current study is distinctive in several respects. First, we assessed the real-world data from the Children’s file. Children, one of the most susceptible subgroups of the population due to their immature systems, are undoubtedly more vulnerable to the health effects of air pollution than adults [18]. Second, our AD diagnosis was confirmed precisely by the
physician, so the potential for selection bias was minimized. Third, in order to identify the dermatologic effect of a single component, our study could be one of the first to investigate the relationship between AD and an active greenhouse gas, CH₄.

Taiwan is located in east Asia, the most polluted region of the world, and is now facing severe air pollution, especially in major urban areas, owing to the rapid increase in population and industrial development, as well as transportation demands [3]. While the number of children with AD continues to increase in both developed and developing countries, the prevalence of AD in Taiwan appears to have grown dramatically over recent decades [19]. According to the Taiwan National Study 2000 to 2007, the overall eight-year prevalence of AD is approximately 6.7%, and has roughly doubled since then [20]. Due to such rapid growth in the number of AD cases with increased urbanization and industrialization, the role of environmental factors, especially airborne pollution, has drawn increasing attention. Over the past ten years, a number of studies have shown that air pollutants, such as PM, TRAP, VOCs, and ETS, are associated with the development and exacerbation of AD. Multiple comprehensive studies have been conducted in the pediatric age group with a large data set. For example, in a French study enrolling 4,907 children who had resided at their current addresses for 3 years or longer, lifetime AD was significantly associated with 3-year averaged concentrations of PM₁₀, NO₂, NOₓ, and CO (adjusted ORs 1.13, 1.23, 1.06, and 1.08, respectively,) [21]. In a Munich prospective birth cohort study including 2,860 children at four years of age demonstrated that NO₂ exposure (per 6.4 mg/m³) was associated with both physician-diagnosed AD and parental reports of symptoms for AD (OR 1.18 and 1.11, respectively,) [22]. In a cross-sectional study during 2011-2012 in Shanghai enrolling 3,358 preschool children indicated that positive correlation between increased gestational and lifetime exposures to a mixture of SO₂, NO₂ and PM₁₀ during total lifetime and childhood AD (ORs 1.78, and 1.87, respectively) [23]. In a US National Survey of Children's Health, 91,642 children found that moderate to severe eczema was associated with elevated levels of NO₃ and PM₂.5 (OR 1.249 and 1.070, respectively,) [24]. A few studies also revealed that prenatal exposure to VOCs and ETS are likely to induce a TH2-dominant immune status or the development of AD after birth [25-27]. In our study, we found that the adjusted HRs for AD increased with the THC (from 1.65 to 10.6), NMHC (from 1.14 to 2.47), and CH₄ (from 1.70 to 11.9) exposure concentrations compared with those exposed to the corresponding concentrations in Q1 level.

Rapid industrialization coupled with urbanization has led to accumulated global waste production because of the continuously increasing demand for energy. Hydrocarbons, organic chemical compounds consisting of hydrogen and carbon, form the basis of the majority of global energy production by fossil fuel combustion and evaporation of gasoline. Both NMHC and CH₄ are composed of THCs. Most hydrocarbons on earth naturally occur from the decomposition of organic matter in petroleum and are generated by human activity. NMHCs, often referred to as VOCs, are unstable forms of substances, such as benzene and their derivatives.

A great number of animal and epidemiological studies have disclosed negative effects of VOCs on skin barrier function. A prospective study in Korea revealed that a 1-ppb increase in outdoor benzene and total VOC concentration were associated with, respectively, 27.38% and 25.86%, respectively, in AD symptoms [11]. Kim et al. also found that exposure to airborne formaldehyde leads to an increase in TEWL and stratum corneum pH both in healthy and AD groups [12]. A rat model of AD conducted by Han et al. showed that formaldehyde exposure aggravated pruritus and skin inflammation. These results suggest that formaldehyde penetrated the injured skin barrier and exacerbated Th1 responses and serum IgE levels in the AD rats [28]. Certain VOCs and
polycyclic aromatic hydrocarbons (PAHs) in several previous studies have been proposed to activate the ligand-activated transcription factor AhR, leading to downstream activation of inflammation and itch mediators such as artemin [29, 30]. CH₄, a nontoxic greenhouse gas, is scarcely reported for other adverse health effects of direct exposure, except for high concentrations leading to suffocation. Our study first identified that CH₄ exposure contributes to an increased risk of AD development. One possible reason for this might be that the extra production of CH₄ from rapid industrialization and urbanization contributes to the higher potential for pathogen transmission [31]. Microbial superinfection leads to an exacerbation of AD [1].

Although our study was a large-scale and population-based cohort, there were still several limitations. First, although AD is a complex and multifactorial disorder, we did not consider other environmental factors, including temperature, humidity, and ultraviolet light that might interact with airborne pollutants. Besides, other potential risk factors for AD, such as atopic family history, dietary factors, pet and prenatal exposure, and even severity of AD could not be estimated in this study due to the lack of information in the children's files. Thirdly, according to our results, a total of 7304 children (2.96%) were diagnosed with AD during the study period. The relatively low prevalence might be attributable to the medical records we chose as our database. Patients with mild AD may neither seek medical services nor be coded for the clinical diagnosis of AD by a physician. In other words, our study population was considerably representative of moderate-to-severe AD presentation of intense itching and relapsing eczematosus skin lesions for more than six months. Finally, we did not investigate indoor air pollution in our study because children have greater participation in the home environment [32].

**Conclusion**

In conclusion, our findings indicated that exposure to higher concentrations of THC, NMHC, and CH₄ might cause an increased risk of AD development. Future studies need to better understand the pathogenesis of air pollutants in AD.

**Abbreviation**

atopic dermatitis (AD); hazard ratio (HR); total hydrocarbon (THC); non-methane hydrocarbon (NMHC); methane (CH₄); particulate matter (PM); nitrogen oxide compound (NOx); environmental tobacco smoke (ETS); volatile organic compounds (VOCs); trans epidermal water loss (TEWL); aryl hydrocarbon receptor (AhR); ozone (O₃); Taiwan National Health Insurance Research Database (NHIRD); International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM); The Taiwan Air Quality Monitoring Network (TAQMN); Taiwan Environmental Protection Administration (TEPA).

**Declarations**

Financial Disclosure:

The authors have indicated they have no financial relationships relevant to this article to disclose.

Competing interests:

None
Data sharing statement:

no additional data

Ethical Approval and Consent to participate:

The data were analyzed anonymously and informed consent is not applicable. This study has been approved by the Institute Review Board of China Medical University Hospital (CRREC-103-048) and complies with the principles outlined in the Helsinki Declaration.

Consent for publication:

This manuscript is an original article that has not been previously published and will not be submitted to any other journal. All the authors have read this manuscript and agree that the work is ready for submission, and accept responsibility for the manuscript's contents.

Availability of data and materials:

Data available on request due to privacy/ethical restrictions.

Funding:

This study is supported in part by Clinical Trial Center and Department of Chinese Medicine and Pharmacy, Ministry of Health and Welfare (MOHW109-TDU-B-212-114004), China Medical University Hospital (CRS-108-015, DMR-HHC-109-9, and DMR-108-200).

Financial Disclosure:

The authors have indicated they have no financial relationships relevant to this article to disclose.

Data sharing statement:

no additional data.

Authors' contributions:

Chang-Ching Wei conceptualized and designed the study. Chieh Wang and Jeng-Dau Tsai drafted the initial manuscript. Cheng-Li Lin carried out the acquisition of data and analysis and interpretation of data. Lei Wan and critically reviewed and revised the manuscript. Chang-Ching Wei coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

References

1. Weidinger S, Novak N: Atopic dermatitis. Lancet (London, England) 2016, 387(10023):1109-1122.
2. Spergel JM, Paller AS: Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003, 112(6 Suppl):S118-127.
3. Eichenfield LF, Hanifin JM, Beck LA, Lemanske RF, Jr., Sampson HA, Weiss ST, Leung DY: Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics* 2003, **111**(3):608-616.
4. Bieber T: *Atopic Dermatitis*. 2008, **358**(14):1483-1494.
5. Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ: Persistence of mild to moderate atopic dermatitis. *JAMA dermatology* 2014, **150**(6):593-600.
6. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA: The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol* 2017, **137**(1):26-30.
7. Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, Gould C, Gemmen E, Dall T: The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *Journal of the American Academy of Dermatology* 2006, **55**(3):490-500.
8. Ahn K: The role of air pollutants in atopic dermatitis. *J Allergy Clin Immunol* 2014, **134**(5):993-999; discussion 1000.
9. Lu C, Deng L, Ou C, Yuan H, Chen X, Deng Q: Preconceptional and perinatal exposure to traffic-related air pollution and eczema in preschool children. *Journal of dermatological science* 2017, **85**(2):85-95.
10. Deng Q, Lu C, Li Y, Sundell J, Dan N: Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environmental research* 2016, **150**:119-127.
11. Kim J, Kim EH, Oh I, Jung K, Han Y, Cheong HK, Ahn K: Symptoms of atopic dermatitis are influenced by outdoor air pollution. *J Allergy Clin Immunol* 2013, **132**(2):495-498.e491.
12. Kim J, Han Y, Ahn JH, Kim SW, Lee SI, Lee KH, Ahn K: Airborne formaldehyde causes skin barrier dysfunction in atopic dermatitis.
13. Hendricks AJ, Eichenfield LF, Shi VY: The impact of airborne pollution on atopic dermatitis: a literature review. *The British journal of dermatology* 2020, **183**(1):16-23.
14. Hassoun Y, James C, Bernstein DI: The Effects of Air Pollution on the Development of Atopic Disease. *Clinical reviews in allergy & immunology* 2019, **57**(3):403-414.
15. He QC, Tavakkol A, Wietecha K, Begum-Gafur R, Ansari SA, Polefka T: Effects of environmentally realistic levels of ozone on stratum corneum function. *International journal of cosmetic science* 2006, **28**(5):349-357.
16. Choi H, Shin DW, Kim W, Doh SJ, Lee SH, Noh M: Asian dust storm particles induce a broad toxicological transcriptional program in human epidermal keratinocytes. *Toxicology letters* 2011, **200**(1-2):92-99.
17. Araviiskaia E, Berardesca E, Bieber T, Gontijo G, Sanchez Viera M, Marrot L, Chuberre B, Dreno B: The impact of airborne pollution on skin. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2019, **33**(8):1496-1505.
18. Annesi-Maesano I, Agabiti N, Pistelli R, Couilliot MF, Forastiere F: Subpopulations at increased risk of adverse health outcomes from air pollution. *The European respiratory journal Supplement* 2003, **40**:57s-63s.
19. Lee YL, Li CW, Sung FC, Yu HS, Sheu HM, Guo YL: Environmental factors, parental atopy and atopic eczema in primary-school children: a cross-sectional study in Taiwan. *The British journal of dermatology* 2007, **157**(6):1217-1224.
20. Yan DC, Ou LS, Tsai TL, Wu WF, Huang JL: Prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2005, 95(6):579-585.

21. Pénard-Morand C, Raherison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, Annesi-Maesano I: Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *The European respiratory journal* 2010, 36(1):33-40.

22. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Krämer U, Behrendt H, Herbarth O, von Berg A, Bauer CP et al: Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 2008, 177(12):1331-1337.

23. Liu W, Cai J, Huang C, Hu Y, Fu Q, Zou Z, Sun C, Shen L, Wang X, Pan J et al: Associations of gestational and early life exposures to ambient air pollution with childhood atopic eczema in Shanghai, China. *The Science of the total environment* 2016, 572:34-42.

24. Kathuria P, Silverberg JI: Association of pollution and climate with atopic eczema in US children. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2016, 27(5):478-485.

25. Herberth G, Bauer M, Gasch M, Hinz D, Röder S, Olek S, Kohajda T, Rolle-Kampczyk U, von Bergen M, Sack U et al: Maternal and cord blood miR-223 expression associates with prenatal tobacco smoke exposure and low regulatory T-cell numbers. *J Allergy Clin Immunol* 2014, 133(2):543-550.

26. Hinz D, Bauer M, Röder S, Olek S, Huehn J, Sack U, Borte M, Simon JC, Lehmann I, Herberth G: Cord blood Tregs with stable FOXP3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year. *Allergy* 2012, 67(3):380-389.

27. Lehmann I, Thoelke A, Rehwagen M, Rolle-Kampczyk U, Schlink U, Schulz R, Borte M, Diez U, Herbarth O: The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. *Environmental toxicology* 2002, 17(3):203-210.

28. Han RT, Back SK, Lee H, Lee J, Kim HY, Kim HJ, Na HS: Formaldehyde-Induced Aggravation of Pruritus and Dermatitis Is Associated with the Elevated Expression of Th1 Cytokines in a Rat Model of Atopic Dermatitis. *PLoS One* 2016, 11(12):e0168466.

29. Mancebo SE, Wang SQ: Recognizing the impact of ambient air pollution on skin health. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015, 29(12):2326-2332.

30. Hidaka T, Ogawa E, Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Fujimura T, Aiba S, Nakayama K, Okuyama R et al: The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin.

31. Neiderud CJ: How urbanization affects the epidemiology of emerging infectious diseases. *Infection ecology & epidemiology* 2015, 5:27060.

32. Breyssse PN, Diette GB, Matsui EC, Butz AM, Hansel NN, McCormack MC: Indoor air pollution and asthma in children. *Proceedings of the American Thoracic Society* 2010, 7(2):102-106.

Tables
Table 1. The demographic information of study population.

|                          | n   | %   |
|--------------------------|-----|-----|
| Gender                   |     |     |
| Boys                     | 126256 | 51.6 |
| Age, years               |     |     |
| ≤ 6                      | 126967 | 51.4 |
| 7-12                     | 101653 | 41.2 |
| >12                      | 18224  | 7.38 |
| Monthly income (NTD)†    |     |     |
| < 15,000                 | 205871 | 83.4 |
| 15,000-19,999            | 30871  | 12.5 |
| ≥ 20,000                 | 10102  | 4.09 |
| Urbanization level&      |     |     |
| 1 (highest)              | 81827  | 33.2 |
| 2                        | 79185  | 32.1 |
| 3                        | 47013  | 19.1 |
| 4 (lowest)               | 38819  | 15.7 |
| Exposure                 |     |     |
| THC level (daily average)| mean, SD | 2.43 | 0.23 |
| NMHC level (daily average)| mean, SD | 0.40 | 0.17 |
| CH4 level (daily average)| mean, SD | 2.03 | 0.13 |
| Follow years             | mean, SD | 10.6  | 3.02 |
| Outcome                  |     |     |
| Atopic dermatitis        | 7304  | 2.96 |

†Monthy income, new Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD.

&: The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

THC, total hydrocarbons; CH4, methane; SD, standard deviation
Table 2. Baseline characteristics of participants exposed to various annual average concentrations of THC

| Variables                          | Q1 N=63003 | Q2 N=60660 | Q3 N=70328 | Q4 N=52853 | p-value |
|------------------------------------|------------|------------|------------|------------|---------|
| Age mean, SD*                      | 5.58       | 5.66       | 7.15       | 7.71       | <0.001  |
| Boys                               | 32841      | 31400      | 36293      | 26722      | <0.001  |
| Monthly income (NTD)†              |            |            |            |            | <0.001  |
| < 15,000                           | 55885      | 53572      | 56140      | 40274      |         |
| 15,000−19,999                      | 5794       | 5428       | 10531      | 9118       |         |
| ≥ 20,000                           | 1324       | 1660       | 3657       | 3461       |         |
| Urbanization level§                |            |            |            |            | <0.001  |
| 1 (highest)                        | 17524      | 13907      | 24184      | 26212      |         |
| 2                                  | 15355      | 24605      | 23393      | 15832      |         |
| 3                                  | 14606      | 10230      | 14777      | 7400       |         |
| 4 (lowest)                         | 15518      | 11918      | 7974       | 3409       |         |
| Outcome                            |            |            |            |            |         |
| Atopic dermatitis                  | 504        | 788        | 2863       | 3149       | <0.001  |

Chi-square test;*One-way ANOVA
Table 3. Baseline characteristics of participants exposed to various annual average concentrations of NMHC

| Variables                  | N=246844 | Q1 N=55312 | Q2 N=75581 | Q3 N=54687 | Q4 N=61264 | p-value |
|----------------------------|----------|------------|------------|------------|------------|---------|
| Age mean, SD*              |          | 6.12       | 3.18       | 6.04       | 3.09       | 7.02    | 3.52    | 6.97    | 3.67    | <0.001  |
| Boys                       |          | 28693      | 51.9       | 39338      | 52.1       | 27917   | 51.1    | 31308   | 51.1    | <0.001  |
| Monthly income (NTD)†      |          |            |            |            |            |         |         | <0.001  |
| < 15,000                   |          | 47529      | 85.9       | 64814      | 85.8       | 44185   | 80.8    | 49343   | 80.5    |         |
| 15,000–19,999              |          | 5766       | 10.4       | 8467       | 11.2       | 7931    | 14.5    | 8707    | 14.2    |         |
| ≥ 20,000                   |          | 2017       | 3.65       | 2300       | 3.04       | 2571    | 4.70    | 3214    | 5.25    |         |
| Urbanization level&        |          |            |            |            |            |         |         | <0.001  |
| 1 (highest)                |          | 10156      | 18.4       | 19922      | 26.4       | 25416   | 46.5    | 26333   | 43.0    |         |
| 2                          |          | 16372      | 29.6       | 26062      | 34.5       | 15707   | 28.7    | 21044   | 34.4    |         |
| 3                          |          | 8878       | 16.1       | 19178      | 25.4       | 9417    | 17.2    | 9540    | 15.6    |         |
| 4 (lowest)                 |          | 19906      | 36.0       | 10419      | 13.8       | 4147    | 7.58    | 4347    | 7.10    |         |
| Outcome                    |          |            |            |            |            |         |         |         |         | <0.001  |
| Atopic dermatitis          |          | 1046       | 1.89       | 1692       | 2.24       | 1878    | 3.43    | 2688    | 4.39    |         |

Chi-square test;*One-way ANOVA
Table 4.
Baseline characteristics of participants exposed to various annual average concentrations of CH4

| Variables                  | Q1     | Q2     | Q3     | Q4     | p-value |
|----------------------------|--------|--------|--------|--------|---------|
| Age mean, SD*              | 5.72   | 5.68   | 6.30   | 8.25   | 4.03    | <0.001  |
| Boys                       | 30067  | 32576  | 32959  | 31654  | <0.001  |
| Monthly income (NTD) †     |        |        |        |        | <0.001  |
| < 15,000                   | 50495  | 55406  | 54061  | 45909  | 73.4    |
| 15,000-19,999              | 6026   | 5210   | 7732   | 11903  | 19.0    |
| ≥ 20,000                   | 1311   | 1784   | 2242   | 4765   | 7.61    |
| Urbanization level &       |        |        |        |        | <0.001  |
| 1 (highest)                | 17455  | 19681  | 23868  | 20823  | 33.3    |
| 2                          | 14939  | 22318  | 22219  | 19709  | 31.5    |
| 3                          | 14376  | 11388  | 10443  | 10806  | 17.3    |
| 4 (lowest)                 | 11062  | 9013   | 7505   | 11239  | 18.0    |
| Outcome                    |        |        |        |        | <0.001  |
| Atopic dermatitis          | 482    | 921    | 1713   | 4188   | 6.69    |

Chi-square test;*One-way ANOVA
| Pollutant levels | Event | PY   | IR      | cHR  | 95%CI       | aHR | 95%CI       |
|------------------|-------|------|---------|------|-------------|-----|-------------|
| THC              | Q1    | 63003| 504     | 0.69 | Ref.        |     | Ref.        |
| Q2               | 60660 | 788  | 694338  | 1.13 | 1.64 (1.47, 1.83) | 1.65 | (1.47, 1.84) |
| Q3               | 70328 | 2863 | 695742  | 4.12 | 5.72 (5.21, 6.29) | 6.43 | (5.85, 7.07) |
| Q4               | 52853 | 3149 | 487850  | 6.45 | 8.82 (8.03, 9.69) | 10.6 | (9.60, 11.6) |
| NMHC             | Q1    | 55312| 1046    | 1.72 | Ref.        |     | Ref.        |
| Q2               | 75581 | 1692 | 834767  | 2.03 | 1.18 (1.09, 1.27) | 1.14 | (1.06, 1.24) |
| Q3               | 54687 | 1878 | 551734  | 3.40 | 1.92 (1.78, 2.07) | 1.93 | (1.79, 2.09) |
| Q4               | 61264 | 2688 | 614430  | 4.37 | 2.48 (2.31, 2.66) | 2.47 | (2.29, 2.66) |
| CH4              | Q1    | 57832| 482     | 0.73 | Ref.        |     | Ref.        |
| Q2               | 62400 | 921  | 713125  | 1.29 | 1.79 (1.60, 1.99) | 1.70 | (1.52, 1.89) |
| Q3               | 64035 | 1713 | 689674  | 2.48 | 3.38 (3.05, 3.73) | 3.32 | (3.00, 3.67) |
| Q4               | 62577 | 4188 | 541086  | 7.74 | 9.99 (9.09, 11.0) | 11.9 | (10.8, 13.1) |

PY = person-years.

IR = Incidence rate, (per 1,000 person-years).

cHR = crude hazard ratio.

aHR = adjusted hazard ratio of a multivariate analysis, after adjustment for age, sex, monthly income, and urbanization level

CI = confidence interval.

Ref. = reference group