Associations of wheeze during the first 18 months of life with indoor nitrogen dioxide, formaldehyde, and family history of asthma: a prospective cohort study

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KEY MESSAGES

1. Wheeze is common among infants and toddlers; recurrent wheeze may indicate underlying asthma.
2. A family history of asthma increases the risk of new onset wheeze.
3. Indoor exposure to formaldehyde is associated with the risk of new onset wheeze, with a 2% increase for each 10-unit increase in formaldehyde.
4. Prevention measures to reduce formaldehyde exposure may reduce wheezy attacks and related disease burden in youngsters.

Hong Kong Med J 2019;25(Suppl 3):S20-3
HHSRF project number: 10110851

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Introduction

Wheezing is common in infants and children. It is defined as a whistling sound that signifies small airway narrowing. Infants with recurrent wheezy attacks may be at risk for developing asthma.[1] Early childhood exposure to various environmental triggers may be an important risk factor for sensitisation and asthma exacerbation.[2] However, discrepancy in association between studies can be explained by different study designs and methods used to document environmental pollutant exposure. A systematic review identified seven studies on the association between formaldehyde exposure and asthma in children, but given the heterogeneity in the definition of asthma and cross-sectional design of the studies, further well-designed prospective epidemiological studies are needed.[2] Of 11 population-based studies that examined indoor NO_2 exposure and asthma onset in children, two reported a positive association and the remaining failed to document any association.[3]

In our previous study to examine simultaneous effects of indoor formaldehyde and NO_2 on wheezing in 528 subjects, indoor exposure to formaldehyde was associated with an increased risk of new onset wheeze. In the present study, we increased the sample size and thus statistical power in examining the association between exposure to formaldehyde and NO_2, onset of wheeze in young children during their first 18 months of life and family history of asthma or non-asthma allergy, after adjusting for confounding factors. Exposure to indoor gaseous pollutants is a modifiable environmental factor. Preventive measures can reduce disease burden of wheezing and possibly asthma in the population.

This study aimed: (1) to examine in infants whether exposure to formaldehyde ≥60 μg/m^3 would increase their risk of wheezing; (2) to examine whether infants exposed to NO_2 had an increased risk of wheezing; and (3) to evaluate if the above associations were modified by a family history of asthma and non-asthma allergy.

Methods

This was a prospective longitudinal study of a cohort of infants from around age 4 months to 18 months recruited from 14 maternal and child health centres between 1 September 2013 and 30 April 2014. Baseline information was collected using the validated International Study of Asthma and Allergies in Childhood questionnaire. Formaldehyde and NO_2 exposure was assessed at age 6 months. Monthly telephone health survey and weekly respiratory health diary by parents were conducted until age 18 months. New onset wheeze between age 6 and 18 months was the primary outcome measure.

Inclusion criteria were: (1) locally born ethnic Chinese, (2) age ≤4 months, (3) birth weight ≥2.5 kg, (4) gestation ≥36 weeks, (5) being taken care of at home by parents or grandparents, (6) telephone number(s) available for follow-up, (7) mother aged ≥18 years, and (8) Cantonese speaking. Exclusion

criteria were: (1) any congenital disease, (2) placement of child in day care centre for >20 hours per week, and (3) moving homes after recruitment.

The International Study of Asthma and Allergies in Childhood questionnaire included 14 family and 18 environmental exposure characteristics and was modified for use in infants. A total of 29 potential confounders were examined, including sex, breastfeeding, neo-natal respiratory illness (excluding wheezing and persistent cough), having sibling(s) in family, sibling with asthma, sibling with allergy, maternal asthma, maternal allergy, and father asthma, father allergy, family history of health status, monthly family income, maternal education, living area, cooking fuel, provision of artificial ventilation during cooking, air conditioning, heater, heating fuel, cockroach infestation, keeping dogs and cats, renovation and/or new furniture within the past 12 months, smoking during pregnancy, maternal or female guardian smoking, father or male guardian smoking, home smokers, proximity to traffic, burning of incense, and burning of mosquito coils.

NO_2 exposure was assessed using the standard diffusion method according to British Standard BS EB 13528-2003. The optimal exposure period of 10 to 14 days allowed detection of NO_2 at domestic level with <5% deviation. The diffusion tube had 71-mm diffusion path length and 10-mm diameter of exposure area, and it was the most commonly used measurement tube.

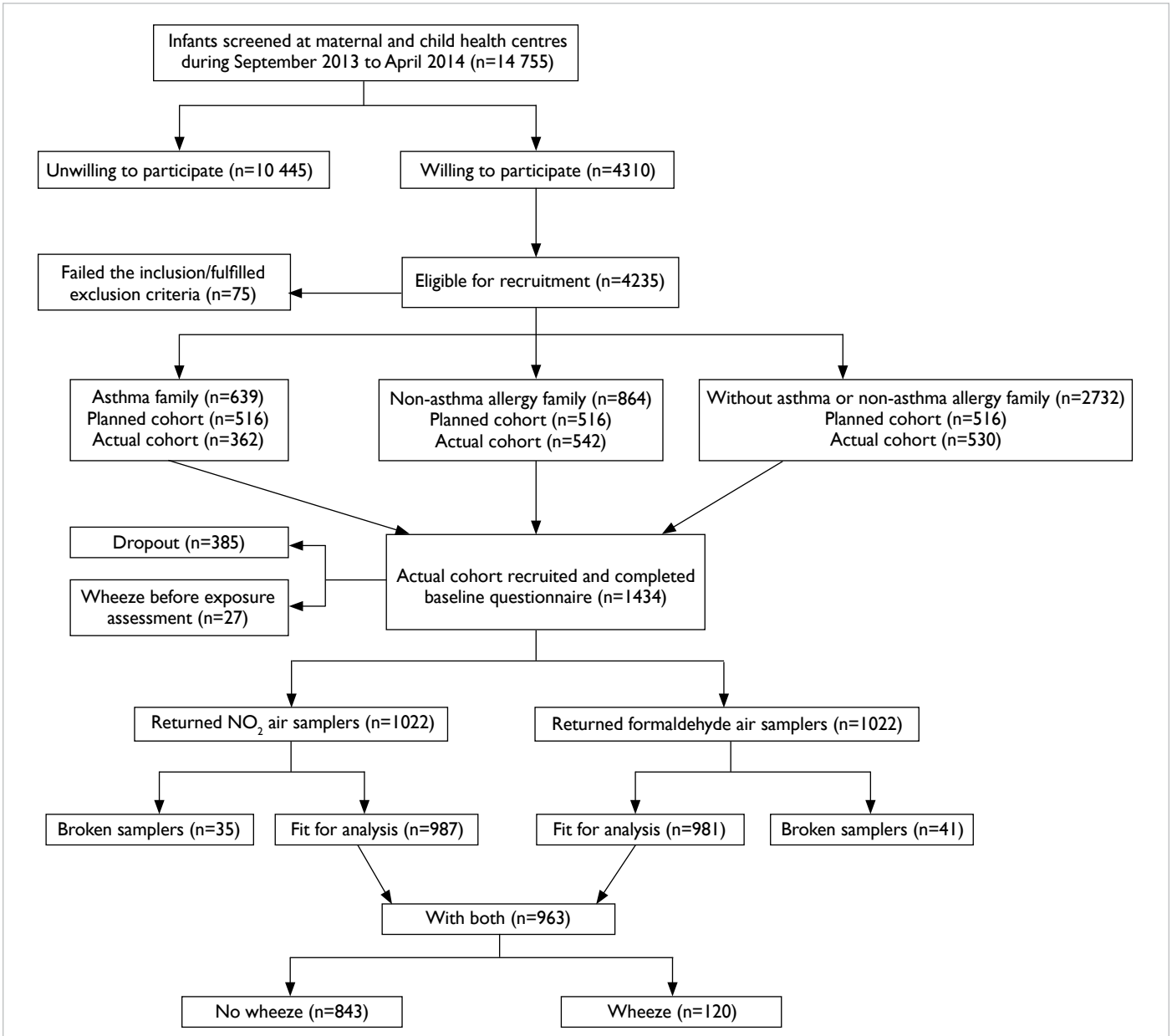

FIG. Flowchart illustrating recruitment and follow-up of subjects

TABLE. Exposure-response relationship between formaldehyde, NO_2 and new onset of wheeze

Factors	Adjusted hazard ratio (95% confidence interval)	P value
Formaldehyde (μg/m³)	1.002 (1.001-1.003)	<0.001
NO_2 (μg/m³)	1.001 (0.995-1.001)	0.692
Sex		
Female	1.000	
Male	1.247 (0.867-1.793)	0.230
Neo-natal respiratory illness		
No	1.000	
Yes	2.281 (0.710-0.732)	0.166
Sibling		
No	1.000	
Yes	1.604 (1.108-2.321)	0.012
Keeping pets		
No	1.000	
Yes	1.371 (0.885-2.125)	0.158
Cooking fuel		
No	1.000	
Yes	0.697 (0.440-2.125)	0.158
Family history		0.021
Healthy	1.000	
Non-asthma allergy	1.059 (0.671-1.673)	0.805
Asthma	1.717 (1.077-2.737)	0.023

Formaldehyde exposure was assessed using the standard diffusion method according to International Standard ISO 16000-4: indoor air–part 4 with an optimum exposure period of 72 hours to detect the domestic level. A standardised self-constructed diffusive sampler in the form of a circular case was used, with a 10-mm diffusion path length and 37-mm diameter of exposure area.

The primary outcome was new onset wheeze. A weekly respiratory health diary was completed by parents to record wheeze as confirmed by a physician. Trained student helpers blinded to the exposure measurements contacted the family on a monthly basis to record any new onset of wheeze and respiratory symptoms in the preceding month. Special attention was paid to note the date of first onset of wheezing.

All data was analysed using the SPSS (Windows version 21; IBM Corp, Armonk [NY], US). To shortlist the possible confounders for new onset of wheezing, the P value of 29 sociodemographic factors and the frequency of event of new onset wheezing were evaluated using the log-rank test, which aimed to provide a notion for pre-selection of possible confounders and the significant level was set at P≤0.25. To evaluate the association of risk factors and new onset of wheezing, the Cox PH model with a backward stepwise method was used. The best combination of possible confounders as identified by log-rank test was achieved by first entering NO_2 and formaldehyde as continuous variables in block 1, and then by uploading all pre-selected possible confounders in categorical variables in block 2. The adjusted hazard ratios (HRs) with 95% confidence interval (CI) for NO_2 and formaldehyde associated with new onset of wheezing were then obtained. With regard to the effect modification and exposure-response relationship, the Cox PH model was used to compute the hazard ratios and 95% CIs of new onset of wheezing for the possible confounders with the risk factors of NO_2 and formaldehyde transformed into categorical variables after sensitivity test.

Results

Of 14755 infants aged ≤4 months screened, only 4235 whose parents consented (participation rate, 28.7%). The final cohort included 228 subjects with a family history of asthma, 384 with a family history of non-asthma allergy, and 351 without family history of any allergies (Fig). During the observation period, 120 (12.5%) subjects had new onset wheezing at a mean age of 13.2 months.

After controlling for possible confounders with a stepwise approach, indoor exposure to formaldehyde increased the risk of new onset wheeze by 2.0% (95% CI=1.0%-3.0%, P<0.001) per 10 units (μg/m³). A family history of asthma also increased the risk of new onset wheeze (adjusted HR=1.72, 95% CI=1.08-2.74, P=0.023). Having sibling(s) also increased the risk of new onset of wheezing (adjusted HR=1.60, 95% CI=1.11-2.32, P=0.01). Indoor exposure to NO_2, sex, cooking fuel, and keeping pets did not have any significant effect on the risk (Table).

Discussion

Indoor exposure to formaldehyde significantly increased the risk of new onset wheeze by 2.0% to 3.0% per 10 units (μg/m³) increase. However, indoor exposure to NO_2 did not pose any significant risk of new onset wheezing. Although furniture made of particle boards or pressed wood products are regarded as the most common source of indoor formaldehyde, our study suggested emission of formaldehyde from other unknown sources. Infants expose to such unknown sources of formaldehyde for a long period may be at increased risk of developing new onset wheezing and subsequent asthma. Opening window to enhance ventilation is effective to get rid of formaldehyde in indoor areas and should be encouraged.

A family history of asthma has been reported as a risk factor for the development of asthma or

wheeze. There was a suggestion that the effects of formaldehyde exposure were strongest in infants without a family history of any allergies. Further studies are required to delineate this complex relationship.

In this study, we excluded two maternal and child health centres located on outlying islands (with different exposure pattern and home environment) and 15 centres located in the city but with heavy workload. The 14 selected centres were scattered throughout Hong Kong to include subjects from different parts of the territory. The participation rate was only 28.7% (n=4235) of all subjects (n=14 755) screened for eligibility, and hence self-selection bias could be an issue. Although the final number of subjects fell short of our target, we could still demonstrate a significant effect of formaldehyde on new onset wheeze. Transient wheezing following viral infection is common in this age group. Longer term follow-up assessment is needed to establish the casual relationship between formaldehyde exposure and asthma development.

Conclusions

Indoor exposure to formaldehyde increased the risk of new onset wheeze in infants aged 6 to 18 months by 2.0% per 10 units ($\mu g/m^3$) of exposure. Indoor exposure to NO_2 did not have any significant effects on the risk. Prevention measures to reduce formaldehyde exposure at home should be implemented. Strategies to reduce indoor concentration of formaldehyde should be promoted. There were suggestions that the association between indoor air pollutants and wheeze/asthma could be modified by a family history of asthma or non-asthma allergies.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#10110851). We thank the Director of Health for granting permission to recruit subjects from maternal and child health centres. We also thank the parents and caregivers for helping to collect air samples and providing health information of their children.

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