Association 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. Indoor exposure to formaldehyde increased the risk of new onset wheezing, and wheezing was more common among infants with a family history of allergy.
2. Indoor exposure to nitrogen dioxide and family history of asthma did not have a significant association with new onset wheezing.
3. Prevention measures to reduce formaldehye exposure in the home environment should be implemented to reduce the future disease burden of asthma in children.
4. If more subjects were recruited for stratified analyses, the possible interactions between family history of asthma or allergy and indoor exposure to formaldehyde on the risk of new onset of wheeze could have been better clarified.

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Introduction

The trend of childhood hospital admissions for asthma has increased in Hong Kong.[1] There is limited evidence of the effect of environmental risk factors on the development of childhood asthma. Environmental exposure to formaldehyde and nitrogen dioxide (NO_2) may increase the risk of childhood asthma. Most studies using a case control or cross sectional study design have shown limited epidemiological evidence of the correct temporal relationship between exposures and asthma, and most have not properly examined the role played by family history of asthma or allergy (confounding vs. effect modification). A prospective cohort design would allow proper examination of the temporal relationship between indoor exposure to air pollutants and incident wheezing or asthma. This study aimed to examine: (1) whether exposure to NO_2 and formaldehyde at home will increase the risk of new onset wheezing in the first 18 months of life; (2) if there is any exposure-response relationship between NO_2 or formaldehyde concentrations and the risk of new onset wheezing; and (3) if the relationship(s) is/are modified by a family history of asthma.

Method

This study was conducted from 1 November 2009 to 30 April 2011. Local Hong Kong infants born between 1 April 2008 and 31 March 2009 who attended any maternal and child health centre, except two on the outlying islands, in Hong Kong were recruited. The sample size was calculated for the birth cohort with NO_2 and formaldehyde as predicator variables and new onset of wheeze as the outcome variable. To facilitate the examination of possible effect modification, eligible subjects were first stratified by family history of asthma or allergy. Roughly equal numbers of infants with a family history of asthma, with a family history of allergy or without any family history of asthma or allergy were recruited. Their parents provided baseline information by completing the validated ISAAC questionnaire before the infants were 4 months old, performed indoor air sampling using standardised passive samplers when the infants were 6 months old, and kept a weekly respiratory health diary and responded to a monthly health telephone survey until the infant was 18 months old. The outcome variable of new onset wheeze was measured between 6 and 18 months of age. We used stepwise Cox-regression models to analyse the associations between exposure to NO_2/formaldehyde and new onset of wheeze (time to event) after controlling for the potential confounders preselected by log rank test. The Cox-regression analysis was repeated in the subgroups of family histories to explore possible effect modifications. Blood samples of subjects with wheeze and a selected sample of subjects without

wheeze were obtained with parental consent to measure eosinophil and immunoglobulin E level to aid in a clinical diagnosis of childhood asthma.

Results

Cohort Subjects

A total of 9321 young infants aged 4 months or younger were screened at 29 maternal and child health centres (excluding two located in the outlying islands with very different living environments). Only 2423 (26%) who fulfilled the inclusion criteria were willing to participate (Fig). A total of 702 subjects were recruited after stratification by family history of asthma and allergy (230 with a family history of asthma, 226 with a family history of allergy, and 246 without any family history of asthma or allergy). 550 subjects completed all observations, but seven subjects who wheezed before the age of 6 months and 15 subjects who provided invalid air samples were excluded. The final cohort included 190 subjects with a family history of asthma, 175 with a family history of allergy, and 163 with no family history of allergy or asthma. During follow-up, 58 (11%) subjects had new onset wheezing at a mean age of 11.4 months.

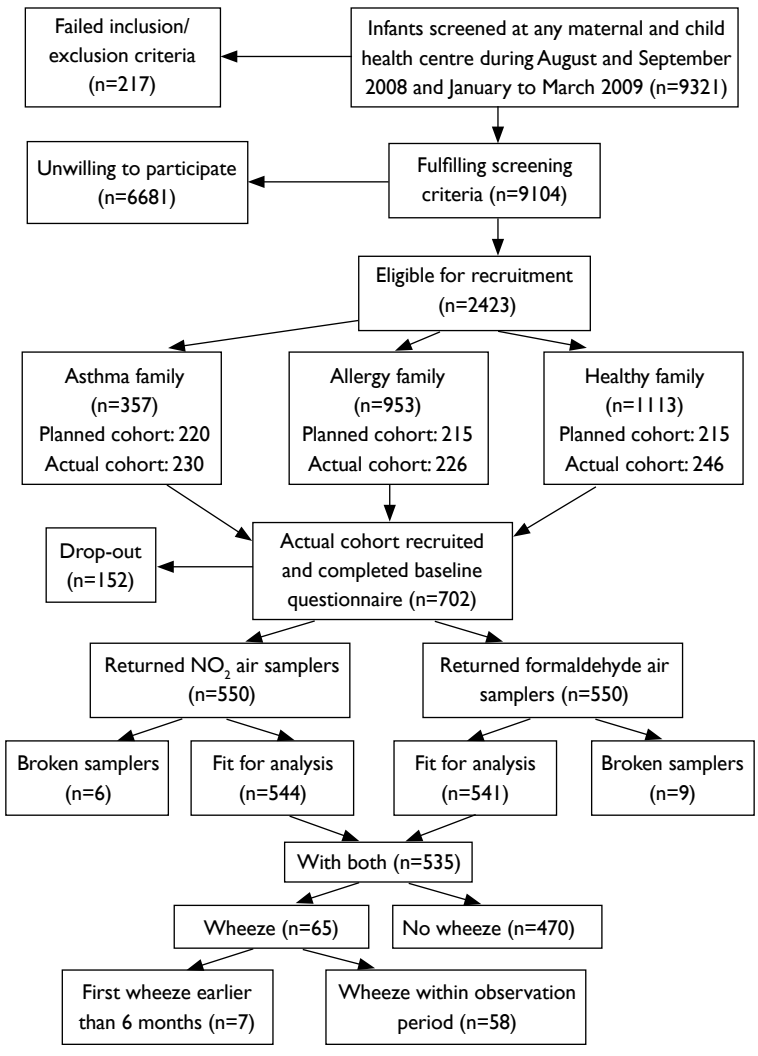

FIG. Flowchart illustrating recruitment and follow-up of cohort subjects

Nitrogen dioxide in bedrooms

In 544 children's bedrooms, the mean indoor NO_2 level was 42.40 (standard deviation [SD], 30.97) μg/m^3. Five samples exceeded the current World Health Organization (WHO) air quality guideline value for 1-hour NO_2 level of 200 μg/m^3 and 227 (42%) samples exceeded the annual average standard of 40 μg/m^3.[2] Paired samples t-test indicated that the indoor NO_2 level in 44 subjects' bedroom in September 2009 (summer) was lower (not significantly) than that in February 2010 (winter) by 5.82 (95% CI= -0.53-12.18) μg/m^3 (P=0.072).

Formaldehyde in bedrooms

In 541 children's bedrooms, the mean indoor formaldehyde level was 51.09 (SD, 74.94) μg/m^3. 94 (17%) samples exceeded the WHO non-industrial indoor formaldehyde exposure standard of 100 μg/m^3.[3] 33 subjects provided measurement of indoor formaldehyde in both winter (February 2009) and summer (May 2009). Wilcoxon signed rank test indicated that the indoor formaldehyde concentration measured in summer was lower (not significantly) than that in winter (P=0.11).

Medical assessment

A total of 112 medical appointments (for 48 wheezing and 64 non-wheezing subjects) were made when infants were 18 months old. The paediatrician was blinded to the health status of subjects recorded in the health diaries. Of the 48 subjects with wheeze, half were diagnosed with asthma. Of the 64 subjects with no wheeze, eight (12.5%) were diagnosed as likely to have asthma. The overall concordance proportion was 80/112 (71.4%) with a fair kappa of 0.39. Only 95 and 93 blood samples were valid for testing immunoglobulin E and eosinophil, respectively. The mean immunoglobulin E was 94.79 (SD, 166.72; range, 1195) kIU/l. The mean eosinophil count was 4.09 (SD, 3.00; range, 16.00) %. Mann-Whitney *U* test indicated that there was no significant difference in the level of immunoglobulin E and eosinophil count between the wheezing and non-wheezing groups.

Association between socio-demographic home environment factors and new onset wheeze

The associations between 27 socio-demographic or home environment factors and new onset of wheeze were tested by log-rank test (Table 1); 11

TABLE 1. Association between socio-demographic factors and new onset of wheeze in the first 18 months of life

Factor	Count*	No. (%) of wheeze		P value (log rank test)
		No event	event	
All infants	543	484 (89.1)	59 (10.9)	
Gender				0.927
Girl	261	233 (89.3)	28 (10.7)	
Boy	282	251 (89.0)	31 (11.0)	
Breastfeeding				0.228
No	107	92 (86.0)	15 (14.0)	
Yes	436	392 (89.9)	44 (10.1)	
Neo-natal respiratory illness				0.007
No	530	475 (89.6)	55 (10.4)	
Yes	13	9 (69.2)	4 (30.8)	
Sibling				0.044
No	315	288 (91.4)	27 (8.6)	
Yes	228	196 (86.0)	32 (14.0)	
Sibling with asthma				0.573
No	516	459 (89.0)	57 (11.0)	
Yes	27	25 (92.6)	2 (7.4)	
Sibling with allergy				0.064
No	473	426 (90.1)	47 (9.9)	
Yes	70	58 (82.9)	12 (17.1)	
Maternal asthma				0.940
No	453	404 (89.2)	49 (11.8)	
Yes	90	80 (88.9)	10 (11.1)	
Maternal allergy				0.216
No	395	356 (90.1)	39 (9.9)	
Yes	148	128 (86.5)	20 (13.5)	
Father asthma				0.183
No	454	401 (88.3)	53 (11.7)	
Yes	89	83 (93.3)	6 (6.7)	
Father allergy				0.957
No	399	356 (89.2)	43 (10.8)	
Yes	144	128 (88.9)	17 (11.1)	
Family history				0.065
Healthy	164	150 (91.5)	14 (8.5)	
Atopy	184	156 (84.8)	28 (15.2)	
Asthma	195	178 (91.3)	17 (8.7)	
Monthly family income (HK$)				0.886
<10 000	45	40 (88.9)	5 (11.1)	
10 000-20 000	136	121 (89.0)	16 (11.0)	
>20 000	362	323 (89.2)	39 (10.8)	
Maternal education				0.650
Primary	13	11 (84.6)	2 (15.4)	
Secondary	268	242 (90.3)	26 (9.7)	
College, university or tertiary education	262	231 (88.2)	31 (11.8)	
Living area (ft^2)				0.115
<600	298	260 (87.2)	38 (12.8)	
600-1000	216	197 (91.2)	19 (9.8)	
>1000	29	27 (93.1)	2 (6.9)	
Cooking fuel				0.106
Electric	50	48 (96.0)	2 (4.0)	
Gas	493	436 (88.4)	57 (11.6)	
Artificial ventilation during cooking				0.544
No	16	15 (93.8)	1 (6.2)	
Yes	527	469 (89.0)	58 (11.0)	
Provision of air conditioning				0.843
No	31	28 (90.3)	3 (9.7)	
Yes	512	456 (87.9)	56 (12.1)	
Provision of heater				0.646
No	228	205 (89.9)	23 (10.1)	
Yes	315	279 (88.6)	36 (11.4)	
Heating fuel				-
Electric	315	279(88.6)	36 (11.4)	
Gas	0			
Cockroach infestation				0.585
No	343	308 (89.8)	35 (10.2)	
Yes	200	176 (88.0)	24 (12.0)	
Keeping pets (cats & dogs)				0.064
No	473	417 (88.2)	56 (11.8)	
Yes	70	24 (95.7)	3 (4.3)	
Renovation and/ or new furniture in past 12 months†				0.224
No	238	208 (87.4)	30 (12.6)	
Yes	305	276 (90.5)	29 (9.5)	
Pregnancy cigarette smoking				0.334
No	535	476 (89.0)	59 (11.0)	
Yes	8	8 (100)	0 (0)	
Maternal or female guardian cigarette smoking				0.954
No	525	468 (89.1)	57 (10.9)	
Yes	18	16 (88.9)	2 (11.1)	
Father or male guardian cigarette smoking				0.481
No	432	383 (88.7)	49 (11.3)	
Yes	111	101 (91.0)	10 (9.0)	
Number of home smokers				0.295
No	442	391 (88.5)	51 (11.5)	
Yes	101	98 (92.1)	8 (7.9)	
Proximity to traffic				0.465
0=never	39	35 (89.7)	4 (10.3)	
1=seldom	274	248 (90.5)	26 (9.5)	
2=often	153	131 (85.6)	22 (14.4)	
3=whole day	77	70 (90.9)	7 (9.1)	

* Seven subjects with wheezing onset before 6 months were excluded

† Only 18 subjects had wall and floor renovations alone; a positive answer to any of the two questions would be regarded as positive for the final variable

were associated with new onset of wheeze with a P value ≤0.25. They were breastfeeding, neonatal respiratory illness (excluding wheezing and persistent cough), having sibling(s), sibling with allergy, maternal allergy, father with asthma, family history of allergy/asthma, living area, cooking fuel, keeping pets, and renovation and/or new furniture in the past 12 months.

Exposure-response relationship between nitrogen dioxide, formaldehyde, and new onset of wheeze

The correlation between NO_2 and formaldehyde was weak with a Spearman's rho of –0.071 (P=0.1). Therefore both independent variables for NO_2 and formaldehyde were entered simultaneously into the Cox's model. Using a stepwise approach, six possible confounders were adjusted in the final model; indoor exposure to formaldehyde significantly increased the risk of new onset wheeze by 4% (95% CI=1-7%, P=0.02) per 10 units (μg/m^3), as did a family history of allergy (hazard ratio=2.21, 95% CI=1.14-4.25, P=0.02) [Table 2]. Indoor exposure to NO_2 had no significant effect on risk. Subgroup analyses showed that a family history of asthma did not modify the risk of new onset wheezing associated with exposure to either NO_2 or formaldehyde. Nonetheless, infants with a family history of allergy were marginally more sensitive to the effect of formaldehyde exposure, with an increased risk of 5% (95% CI=1-8%) for new onset wheeze per additional 10 units (μg/m^3) of exposure.

TABLE 2. Exposure-response relationship between nitrogen dioxide, formaldehyde, and new onset of wheeze

Factor	Adjusted hazard ratio (95% CI)	P value
Formaldehyde	1.004 (1.001-1.007)	0.016
Nitrogen dioxide	0.991 (0.979-1.003)	0.128
Neo-natal respiratory illness (excluding wheezing or persistent cough)		
No	1.000	
Yes	4.133 (1.476-11.576)	0.007
Having sibling(s)		
No	1.000	
Yes	1.871 (1.096-3.193)	0.022
Family history		
Healthy	1.000	
Allergy	2.205 (1.144-4.250)	0.018
Asthma	1.091 (0.533-2.234)	0.812
Living area (ft^2)		
<600	1.000	
600-1000	0.546 (0.304-0.981)	0.043
>1000	0.357 (0.083-1.533)	0.166
Keeping pets		
No	1.000	
Yes	0.423 (0.128-1.395)	0.158
Cooking fuel in household		
Electric	1.000	
Gas	3.235 (0.782-13.388)	0.105

Discussion

Effects of exposure to indoor pollutants

After controlling for confounders, the risk of new onset wheezing in young infants was associated with indoor exposure to formaldehyde, with the risk increased by 4% for every 10-unit increase (μg/m^3). Indoor exposure to NO_2 did not pose a significant risk for new onset wheezing in the first 18 months.

This was the first prospective cohort study to report a significant quantitative association between indoor exposure to formaldehyde and risk of new onset wheeze in young children after adjustment for major potential confounding factors. Our results provide further support of the possible causal relationship between domestic exposure to formaldehyde and the induction of asthma in children.

Indoor exposure to NO_2 at levels between 40 and 45 μg/m^3 has been found to be associated with asthma in asthmatic children,[4] but this was not confirmed in the present study. It is possible that NO_2 at relatively low levels between 40 and 45 μg/m^3 can exacerbate asthma in children with pre-existing asthma, but not directly induce wheezing/asthma in naïve subjects.

Effect modification by family history of asthma and family history of allergy

A family history of asthma has been established as a risk factor for asthma or wheeze in many studies,[5] but it was not confirmed in the present study. Infants with a family history of allergy, including parents or a sibling diagnosed with allergy, had an increased risk of new onset wheezing in the present study. The effect of formaldehyde exposure was stronger in infants with a family history of allergy. Effect modification by family history of asthma and family history of allergy was explored, but the inadequate sample size after stratification did not allow proper examination of possible interactions. If more subjects were recruited for the stratified analyses, the possible interactions between family history of asthma or allergy and indoor exposure to formaldehyde and their effect on the risk of new onset of wheeze could have been better clarified.

Limitations

The study subjects might not be representative of all

infants born in Hong Kong. Although recruitment from 29 maternal and child health centres (excluding two located in outlying islands with very different living environments) was reasonably representative, the participation rate was <30%, and self-selection bias could have occurred.

The outcome of wheeze was reported by parents and not objectively observed or verified. Over or under reporting was possible. Exposure to NO_2 and formaldehyde was assessed by standard methods, but the one-off measurement might not have been representative of exposure throughout the observation or follow-up period. Subgroups with paired samples during summer and winter months indicated that the seasonal variation in indoor concentrations of NO_2 and formaldehyde was not significant.

Our study had insufficient statistical power for subgroup analyses as a result of overestimation of the occurrence of wheezing (using prevalence in older children to estimate incidence of new onset wheezing in young infants), as well as the lack of full compliance with air sampling.

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References

1. Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. Clin Exp Allergy 2006;36:1138-46.
2. World Health Organization. Health aspects of air pollution with particulate matter, ozone and nitrogen dioxide. Bonn, Germany; 13-15 January 2003.
3. Liteplo RG, Beauchamp R, Meek ME, Chenier R. Concise International Chemical Assessment Document 40, Formaldehyde. Geneva: World Health Organization, 2002. Available from http://www.inchem.org/documents/cicads/cicads/cicad40.htm.
4. Mi YH, Norback D, Tao J, Mi YL, Ferm M. Current asthma and respiratory symptoms among pupils in Shanghai, China: influence of building ventilation, nitrogen dioxide, ozone, and formaldehyde in classrooms. Indoor Air 2006;16:454-64.
5. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am J Respir Crit Care Med 1999;160:227-36.