

Ambient Formaldehyde Levels and Allergic Disorders Among Japanese Pregnant Women: Baseline Data From the Osaka Maternal and Child Health Study

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PURPOSE: The effects of formaldehyde (FA) exposure on allergic disorders are not clearly understood. This cross-sectional study examined the relationship between FA exposure and the prevalence of allergic disorders in Japan.

METHODS: Subjects were 998 pregnant women. Participants were considered to have asthma, atopic eczema, or allergic rhinitis (including cedar pollinosis) if they had received any medical treatment for any of these allergic disorders during the previous 12 months. Passive air sampling tubes were worn for 24 hours and analyzed for FA.

RESULTS: When FA levels were categorized into four groups, there was a tendency for a positive exposure-response relationship between FA levels and the prevalence of atopic eczema, although the adjusted odds ratio for highest vs. lowest FA categories did not reach statistical significance. When FA levels were categorized into two groups to assess the effects of exposure to high levels of FA on allergic disorders, FA levels of 47 ppb or more were independently associated with an increased prevalence of atopic eczema (adjusted odds ratio = 2.25; 95% confidence interval, 1.01–5.01). The positive association was more pronounced in women with a negative familial allergic history than in those with a positive familial allergic history. No clear association was found between FA levels and the prevalence of asthma or allergic rhinitis.

CONCLUSIONS: FA exposure may be associated with an increased prevalence of atopic eczema in Japanese pregnant women.

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INTRODUCTION

A worldwide increase in allergic disorders in both children (1–3) and adults (4, 5) has been observed during the past few decades. A number of causes have been proposed for

this increase. They include fewer infections during early childhood (6), exposure to microbial compounds in the environment and underlying innate and adaptive immune responses (7), exposure to cigarette smoke (8) and other outdoor and indoor irritants and allergens (9), and damp housing and the presence of molds in the home (10). However, the etiology of allergic disorders is still not sufficiently well understood.

Because people spend much of their time indoors, exposure to organic chemicals that arise from synthetic materials and furnishings, such as formaldehyde (FA), is inevitable. Several epidemiological studies examined the association between FA exposure and respiratory symptoms and allergic disorders (11–18). A cross-sectional study of Swedish adults showed that FA at home was significantly associated with an increased prevalence of nocturnal breathlessness (11). In another Swedish cross-sectional study, the prevalence of asthma increased among adults with domestic exposure to newly painted indoor surfaces that was related to a significant increase in FA concentrations (12). In contrast, FA

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Selected Abbreviations and Acronyms

FA = formaldehyde
OMCHS = Osaka Maternal and Child Health Study
OR = odds ratio
95% CI = 95% confidence interval

at home was not related to respiratory symptoms or diseases in a U.S. cross-sectional study (13). A cross-sectional study in Swedish school personnel found no relationship between FA in the classroom air and nasal symptoms (14). A case-control study in Australian children showed that FA exposure was positively associated with asthma (15). In a cross-sectional study in Swedish secondary schoolchildren, schools with greater concentrations of FA had more pupils with current asthma (16). A marginally significant positive association was observed among Australian children between FA exposure and the prevalence of atopy, but not asthma or respiratory symptoms (17). There was no relationship between FA and persistent wheezing illness in a case-control study of U.K. children (18).

To our knowledge, no epidemiologic study has assessed the association between FA and atopic eczema all over the world, and there has been no epidemiological information regarding the relationship between FA exposure and allergic disorders in Japan. Using a cross-sectional design, we analyzed baseline data from the Osaka Maternal and Child Health Study (OMCHS) to investigate the association between FA exposure and the prevalence of asthma, atopic eczema, and allergic rhinitis in Japanese pregnant women.

METHODS

Study Population

The OMCHS is an ongoing prospective cohort study that was initiated to investigate preventive and risk factors for maternal and child health problems such as allergic disorders and postpartum depression. The background and general procedure of the OMCHS have been described previously (19). In brief, the subjects, who were pregnant women at enrollment, were asked to complete a baseline survey that was followed by several postnatal surveys. Originally, eligible subjects were restricted to pregnant women in Neyagawa City, which is one of the 43 municipalities in Osaka Prefecture. The Prefecture has a total population of approximately 8.8 million people. Between November 2001 and March 2003, there were 3,639 eligible subjects in Neyagawa City, and 627 pregnant women (17.2%) chose to participate in this study. Because of the low participation rate in Neyagawa City, the opportunity to enroll was extended to eligible subjects who lived in other municipalities in Osaka Prefecture. Eight pregnant women who did not live in Neyagawa City but who learned of the study at an

obstetric clinic before August 2002 participated in this study. In addition, 77 participants who heard the accounts of the OMCHS from public health nurses in six other municipalities from August 2002 to March 2003 were enrolled into the study. From October 2002 to March 2003, 290 participants were recruited from a university hospital and 3 obstetric hospitals in three other municipalities; these women were recommended for participation in the OMCHS by an obstetrician. Finally, a total of 1002 participants gave their fully informed consent in writing and completed the baseline survey. Missing data on FA exposure caused the exclusion of four subjects. There were 998 participants left for analysis. The OMCHS was approved by the ethics committees of the Osaka City University School of Medicine and the Osaka Prefectural Institute of Public Health.

Measurements

After enrollment, each participant completed a set of two self-administered questionnaires. One involved demographic and health indication data, and the other diet history data. The participants were requested to wear a passive diffusion sampling tube to measure FA and nitrogen dioxide and to collect two dust samples of the bedclothes and flooring for the detection of mite antigen. Participants mailed these materials to the data management center. Research technicians reviewed the questionnaire, and missing or illogical data were completed by telephone interview. Data regarding diet and concentrations of nitrogen dioxide were not used in this study because our other papers will report or have reported the associations of these variables with allergic disorders (20–22).

One of the self-administered questionnaires inquired about age; gestation; parity; indoor domestic pets; family income; education; personal history of asthma, atopic eczema, and allergic rhinitis; family history of asthma, atopic eczema, and allergic rhinitis; smoking habits; current passive smoking exposure; and the presence of mold in the kitchen. Current asthma, atopic eczema, and allergic rhinitis (including Japanese cedar pollinosis) were considered present if subjects received any medical treatment for any of these allergic disorders during the previous 12 months. Detailed data on the types of medications and the duration of their use were not collected. A family history of asthma, atopic eczema, and allergic rhinitis (including Japanese cedar pollinosis) was defined as present if a parent or sibling had exhibited any of these doctor-diagnosed allergic disorders.

The passive air sampling tubes contained silica gel impregnated with triethanolamine (Sibata Scientific Technology Co, Ltd, Tokyo, Japan). The sampling tubes were worn for 24 hours and analyzed for FA by a spectrophotometrical method that is highly correlated with results from liquid chromatography (23, 24). Concentrations of FA are

reported in parts per billion (ppb) and represent the mean concentrations for the exposure periods.

Two dust samples were collected from a 1-m² area of the bedclothes and flooring for 1 minute using a vacuum cleaner fitted with a collection apparatus. Antigen levels of *Dermaphagoides farinae* mite from extracts of fine dust fractions were measured with a double-antibody sandwich enzyme-linked immunosorbent assay using a soluble antigen prepared from the whole mite bodies as a reference standard and expressed as antigen equivalent in micrograms per square meter of surface area (Mitey checker; Shinto Fine Co, Ltd, Osaka, Japan) (25, 26). The antigen levels were semi-quantitatively classified with scores of – (<2 µg/m²), ± (5 µg/m²), + (10–15 µg/m²), and ++ (>35 µg/m²). In the present study, we used only results from the bedclothes because the correlation between antigen levels from the bedclothes and flooring was almost collinear (Spearman correlation coefficient = 0.54; *p* < 0.0001).

Statistical Analysis

FA exposure was categorized into four groups. The cut-off points were at the 30th, 60th, and 90th percentile values on the basis of the distribution for all study subjects (<18, 18–27, 28–46, and ≥47 ppb) because the distribution was markedly skewed toward high values (skewness = 1.69, kurtosis = 4.75). Also, FA exposure was classified into two groups using a cut-off point at the 90th percentile to assess the effects of exposure to high levels of FA on allergic disorders. Covariates included in the multivariate models were age (<30 and ≥30 years); gestation (<18 and ≥18 weeks); parity (0 and ≥1); family history of asthma, atopic eczema, and allergic rhinitis; cigarette smoking (never, former, and current); current passive smoking at home and work; mold in the kitchen; indoor domestic pets; family income (Japanese yen <4,000,000, 4,000,000–5,999,999, and ≥6,000,000 / year); education (<13, 13–14, and ≥15 years); mite antigen level in house dust (–, ±, and + or ++); and season when data were collected (spring, summer, fall, and winter).

Logistic regression analysis was used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for allergic disorders in relation to FA levels. To examine whether the prevalence increased with increases in levels of FA, the trend of association was evaluated using a logistic regression model assigning the median value in each exposure category as the representative score. A two-sided *p* value less than 0.05 was considered to indicate statistical significance. Also, an exposure-response relationship was regarded as marginally significant when the *p* value (two-sided) ranged from 0.05 to less than 0.10. We also conducted analyses stratified by a familial allergic history to assess possible effect modification by this variable. Because a familial allergic history is a convincing risk factor for allergic

disorders, FA exposure might be expected to have a smaller effect in the development of allergic disorders among individuals with a positive familial allergic history. The homogeneity of odds ratios between pregnant women with a positive and negative familial allergic history was tested by including an interaction term of a familial allergic history × FA exposure into the model. All computations were performed using the SAS software package version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

The prevalence of current asthma, atopic eczema, and allergic rhinitis was 2.1%, 5.7%, and 14.0%, respectively. About half of the participants were 30 years or older and enrolled by the 17th week of gestation (Table 1). High mite antigen

TABLE 1. Distribution of selected characteristics in 998 pregnant women, Osaka Maternal and Child Health Study, Japan, November 2001 to March 2003

Variable	n (%)
Age, years	
<30	471 (47.2)
≥30	527 (52.8)
Gestation, weeks	
<18	507 (50.8)
≥18	491 (49.2)
Parity ≥1	511 (51.2)
Family history of asthma	101 (10.1)
Family history of atopic eczema	138 (13.8)
Family history of allergic rhinitis	428 (42.9)
Cigarette smoking	
Never	694 (69.5)
Former	120 (12.0)
Current	184 (18.4)
Current passive smoking at home	493 (49.4)
Current passive smoking at work	120 (12.0)
Mold in kitchen	204 (20.4)
Indoor domestic pets (cats, dogs, birds, or hamster)	113 (11.3)
Mite antigen level in house dust ^a	
–	433 (43.4)
±	297 (29.8)
+ or ++	268 (26.9)
Family income (Japanese yen/year)	
<4,000,000	298 (29.9)
4,000,000–5,999,999	403 (40.4)
≥6,000,000	297 (29.8)
Education, years	
<13	322 (32.3)
13–14	410 (41.1)
≥15	266 (26.7)
Season when data were collected	
Spring	310 (31.1)
Summer	176 (17.6)
Fall	207 (20.7)
Winter	305 (30.6)

^aAntigen levels were semiquantitatively classified with scores of – (<2 µg/m²), ± (5 µg/m²), + (10 to 15 µg/m²), and ++ (>35 µg/m²).

levels of 10 $\mu\text{g}/\text{m}^3$ or greater were measured in the houses of 27% of the participants. The median and maximum level of FA among all participants was 24 and 131 ppb, respectively. A total of 13 samples (1.3%) exceeded the current Japanese indoor guideline of 80 ppb. FA levels varied by season and the highest levels were found during the winter (Kruskal-Wallis test; $p < 0.0001$).

There was a tendency for a positive exposure-response relationship between FA levels and the prevalence of atopic eczema, although the crude OR for highest vs. lowest FA categories did not reach statistical significance (Table 2). Adjustments for age; gestation; parity; family history of asthma, atopic eczema, and allergic rhinitis; cigarette smoking; current passive smoking at home and work; mold in the kitchen; indoor domestic pets; family income; education; mite antigen level in house dust; and season did not appreciably change these results. When FA levels were categorized into two groups using a cut-off point at the 90th percentile, FA levels of 47 ppb or more were independently associated with an increased prevalence of atopic eczema in the multivariate model (adjusted OR, 2.25; 95% CI, 1.01–5.01). The same result was observed if levels of FA were treated as a continuous variable. For every 10-unit (ppb) increase in FA exposure, there was an increase of 16% in the prevalence of atopic eczema (adjusted OR, 1.16; 95% CI, 0.99–1.35). No clear association was found between FA levels and the prevalence of asthma or allergic rhinitis.

When subjects were divided according to familial allergic history in at least one parent or sibling, an increased prevalence of atopic eczema in relation to FA levels was more pronounced in those with a negative than with a positive familial allergic history, after multivariate adjustment (Table 3). This association was marginally significant only among women with a negative familial allergic history. The multivariate OR of atopic eczema for comparison of a positive with a negative familial allergic history was 1.78 (95% CI, 1.01–3.22). No significant interaction was found in the association of FA levels with the prevalence of atopic eczema between pregnant women with a positive and negative familial allergic history ($p = 0.69, 0.44$, and 0.30 for homogeneity of OR for the second, third, and fourth categories, respectively).

DISCUSSION

In the present cross-sectional study of Japanese pregnant women, we found that FA exposure was positively related to the prevalence of atopic eczema, especially in women with a negative familial allergic history. However, no clear association was shown between FA and the prevalence of current asthma or allergic rhinitis.

No epidemiologic studies, to our knowledge, have examined whether there is an association between FA levels and

TABLE 2. Crude and adjusted ORs and 95% CIs for current allergic disorders in relation to formaldehyde exposure levels, Osaka Maternal and Child Health Study, Japan, November 2001 to March 2003

Formaldehyde levels (ppb)	Prevalence (%)	Crude		Adjusted ^a	
		OR (95% CI) ^b	OR (95% CI) ^c	OR (95% CI) ^b	OR (95% CI) ^c
Asthma					
<18	7/298 (2.4)	1.00		1.00	
18–27	6/299 (2.0)	0.85 (0.28–2.56)	1.00	0.80 (0.23–2.84)	1.00
28–46	5/301 (1.7)	0.70 (0.22–2.24)		0.72 (0.19–2.77)	
≥47	3/100 (3.0)	1.29 (0.33–5.07)	1.51 (0.44–5.23)	2.15 (0.41–11.28)	2.65 (0.63–11.11)
		(p for trend = 0.87)		(p for trend = 0.47)	
Atopic eczema					
<18	15/298 (5.0)	1.00		1.00	
18–27	15/299 (5.0)	1.00 (0.48–2.08)	1.00	1.03 (0.47–2.29)	1.00
28–46	17/301 (5.7)	1.13 (0.55–2.31)		1.11 (0.50–2.42)	
≥47	10/100 (10.0)	2.10 (0.91–4.83)	2.01 (0.98–4.12)	2.36 (0.92–6.09)	2.25 (1.01–5.01)
		(p for trend = 0.08)		(p for trend = 0.08)	
Allergic rhinitis					
<18	45/298 (15.1)	1.00		1.00	
18–27	41/299 (13.7)	0.89 (0.57–1.41)	1.00	1.06 (0.65–1.73)	1.00
28–46	37/301 (12.3)	0.79 (0.49–1.26)		0.85 (0.51–1.40)	
≥47	17/100 (17.0)	1.15 (0.63–2.12)	1.29 (0.74–2.25)	1.17 (0.60–2.28)	1.22 (0.68–2.20)
		(p for trend = 0.91)		(p for trend = 0.91)	

^aBased on multiple logistic regression controlling for age; gestation; parity; family history of asthma, atopic eczema, and allergic rhinitis; cigarette smoking; current passive smoking at home and work; mold in the kitchen; indoor domestic pets; mite antigen level in house dust; family income; education; and season when data were collected.

^bFormaldehyde levels were categorized into 4 groups using cut-off points at the 30th, 60th, and 90th percentile values.

^cFormaldehyde levels were categorized into 2 groups using a cut-off point at the 90th percentile value.

TABLE 3. Adjusted ORs and 95% CIs for current atopic eczema in relation to formaldehyde exposure levels by familial allergic history, Osaka Maternal and Child Health Study, Japan, November 2001 to March 2003^a

Formaldehyde levels (ppb)	Negative familial allergic history (n = 488)			Positive familial allergic history (n = 510)		
	Prevalence (%)	OR (95% CI) ^b	OR (95% CI) ^c	Prevalence (%)	OR (95% CI) ^b	OR (95% CI) ^c
<18	4/141 (2.8)	1.00		11/157 (7.0)	1.00	
18–27	5/156 (3.2)	1.37 (0.33–5.79)	1.00	10/143 (7.0)	0.80 (0.30–2.12)	1.00
28–46	7/147 (4.8)	1.88 (0.49–7.23)		10/154 (6.5)	0.92 (0.35–2.45)	
≥47	4/44 (9.1)	4.21 (0.90–19.85)	2.96 (0.87–10.12)	6/56 (10.7)	1.45 (0.42–4.93)	1.63 (0.58–4.57)
		(p for trend = 0.06)			(p for trend = 0.50)	

^aBased on multiple logistic regression controlling for age; gestation; parity; cigarette smoking; current passive smoking at home and work; mold in the kitchen; indoor domestic pets; mite antigen level in house dust; family income; education; and season when data were collected.

^bFormaldehyde levels were categorized into four groups using cut-off points at the 30th, 60th, and 90th percentile values.

^cFormaldehyde levels were categorized into two groups using a cut-off point at the 90th percentile value.

atopic eczema. There are potential reasons why such an association may exist. In a climate chamber study, FA exposure induced a significant increase of transepidermal water loss in patients with atopic eczema but not in control subjects (27). The irritant properties of FA may impair the epidermal barrier function (27). In our study, approximately 50% of the participants who had atopic eczema at the time of data collection had been treated with medications before 12 years of age. Therefore, exposure to FA may exacerbate atopic eczema symptoms in adults. Alternatively, the observed association might be attributed to unrecognized environmental factors associated with FA.

A more evident positive relationship between FA and atopic eczema was found in our subjects who had a negative familial allergic history than in those with a positive familial allergic history. A 4-year follow-up study in Swedish school-children showed that among children without a history of atopy a new asthma diagnosis was more common at higher levels of FA in classroom air (28). The present findings are in partial agreement with this observation. Further studies are necessary to understand the interaction between FA and genetic factors in the manifestation of atopic eczema.

We found no significant association between FA and the prevalence of current asthma. The present findings are in agreement with previous observations in the United States showing no association between FA at home and respiratory symptoms or diseases in adults (13) and between exposure to FA vapor and bronchoconstriction among medical students (29). However, they are in disagreement with results of a previous study showing a positive association between FA exposure at home and asthma (12). It may be difficult to detect a clear positive association between FA and current asthma in our study population that had only a few asthmatics.

In our study, no significant association between FA and the prevalence of current allergic rhinitis was detected. As far as we know, only one epidemiologic study has investigated whether there was an association between FA and allergic rhinitis. A cross-sectional study in Sweden found

no association between FA levels in classroom air and nasal symptoms in primary school personnel (14). Their results are compatible with our findings.

Our participants were relatively homogeneous because all were pregnant and we obtained extensive information on potential confounding factors. Although there were 3,639 eligible pregnant women in Neyagawa City, only 627 (17.2%) took part in this study. We do not know if a difference existed between participants and nonparticipants because data on personal characteristics, such as age, socioeconomic status, and history of allergic disorders, were not available for nonparticipants. Regarding the remaining 374 participants who were not residents of Neyagawa City, we could not calculate the participation rate because the exact number of eligible women was not available. Also, we could not compare participants with nonparticipants in the four collaborating hospitals and six municipalities. Because our subjects might not be representative of Japanese pregnant women in general, the present findings cannot be generalized. In fact, educational levels were greater in the present study population than in the general population. According to the 2000 population census of Japan, the proportions of women ages 30 to 34 years in Osaka Prefecture with years of education of <13, 13 to 14, ≥15, and unknown were 49.2%, 32.3%, 13.6%, and 4.9%, respectively (30). The corresponding figures for the present study were 32.3%, 41.1%, 26.7%, and 0.0%, respectively. No attempt was made to ascertain outcome status through reviews of medical records. Moreover, we did not use validated diagnostic criteria for allergic disorders, such as those reported in the International Study of Asthma and Allergies in Childhood. Because the definition of allergic disorders was based on self-reporting and medical treatment in the past 1 year, there was probably a loss of milder cases of allergic disorders. In particular, women who want to become pregnant or who are pregnant might tend to avoid drugs.

The main sources of emission of FA in homes are gas appliances, open fireplaces, tobacco products, furniture, woodchip boards and other building materials containing

FA (31). Asthma, atopic eczema, and allergic rhinitis sufferers might not be aware of the main sources of FA and the possible ill effects of FA exposure. In our study, furthermore, the exposure measurements were performed in parallel with completing the questionnaires, so the former might not be able to influence the reporting of allergic disorders. The consequence would have given rise to an underestimation of our findings because of nondifferential outcome misclassification.

Each participant wore a passive diffusion sampling tube on a usual day, and then the tube was analyzed by laboratory personnel blind to health status to minimize observer bias. Both measurement errors of FA and day-to-day variations in personal exposures would have most probably led to non-differential exposure misclassification.

The interface between allergy/immunology and pregnancy should be discussed, which may have an influence on the association of interest. It has been suggested that pregnancy involves a shift to the Th2 side of the immune response (32) whereas the importance of the role of NK and interleukin (IL)-12, IL-15, and IL-18 tripods in successful or failed pregnancy in humans was suggested beyond the Th1/Th2 paradigm (33). Pregnancy does not appear to have a consistent effect on the frequency or severity of asthma (34). Rhinitis symptoms during pregnancy may be attributable to the hormonal changes in pregnancy. However, rhinitis solely ascribed to pregnancy may not be a distinct entity because most pregnant women do not have significant nasal symptoms (33). Symptoms of atopic eczema may worsen with pregnancy in some patients and appear to improve in others (35). Atopic eczema in pregnancy is not likely to be a distinct entity. Regarding the interpretation and generalization of our results, the interface between allergic disorders and pregnancy is likely to be a minor problem.

This is the first epidemiological study on the association between exposure to FA and allergic disorders in Japan. Because this was a cross-sectional study, we could not establish a cause and effect relationship for the associations under study. Further evaluations in prospective studies are needed to draw a conclusion regarding whether FA exposure increases the likelihood of atopic eczema.

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APPENDIX

Space limitations preclude the inclusion as authors of the following members of the Osaka Maternal and Child Health Study Group:

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