either rapid or slow acetylators, depending on their ability to acetylate certain NAT substrates. Generally, acetylation is bimodally distributed in different populations. An association between NAT2 slow acetylation and allergic diseases and extrinsic asthma in patients with atopic characteristic has been reported.[187,188]

Certain genes within the *GSTM*, *GSTT* and *GSTP* subfamilies (*GSTM1*, *GSTT1* and *GSTP1*) are polymorphic in humans and the levels of individual enzymes expressed can be influenced by induction and genetic polymorphism. The *GSTM1*, *GSTT1* and *GSTP1* genes are located on chromosomes 1p13.3, 22q11.23 and 11q13, respectively. Lack of GSTM1 and GSTT1 activity is caused by the homozygous deletion of these intact genes (the null genotype). The non-null genotype is the wild type or heterozygote. The 1404A > G (Ile105Val) and 2294C > T (Ala114 Val) SNPs of the *GSTP1* gene confers lower levels of enzyme activity toward a variety of carcinogens and anticancer agents. As compared with the combined *GSTM1* non-null genotype (*GSTT1* non-null genotype and *GSTP1* AG), the combined *GSTM1* null genotype (*GSTT1* null genotype and *GSTP1* AA) was associated with a significantly increased risk of AD (OR = 9.43, 95% CI = 1.06–438.6).[189]

NAT2 gene maps on chromosome 8p23.1–p21.3. It covers 9.97 kb on the direct strand. N-acetylation is an important genetic polymorphic pathway in the biotransformation of one or more single-based mutations in the *NAT2* gene known to cause low expression levels of functional *NAT2* enzyme.[190,191] Individuals who carry two slow *NAT2* SNPs are slow acetylators, whereas those who are homozygous or heterozygous for wild-type *NAT2* alleles are rapid acetylators.[192,193] The presence of 481C > T, 590 G > A and 857G > A SNPs would lead to slow acetylation.[194] 481C > T (synonymous mutation) and 590G > A SNPs were not related to an increased risk of AD.[195] Moreover, 481C > T, 590 G > A and 857G > A, were not associated with an increased risk of AD.[196]

DISCUSSION AND CONCLUSION

The most important problems facing AD research are identifying "at-risk" individuals and implementing clinical surveillance, prevention practices, and follow-up care. The immune system plays an important role in AD. Although the increased/decreased risk associated with individual immune system SNPs may be small compared to that conferred by high-penetrance cancer genes, their public health implications may be large because of their high frequency in the general population. It is thus essential that epidemiological investigations of immune system polymorphisms are adequately designed. Unfortunately a fairly large number of studies are limited by their sample size and subsequently suffer from lack of power to detect effects that may truly exist. Also, given the borderline significance of previously reported associations and multiple comparisons, it is possible that one or more findings are false-positives.[197] Large and combined analyses may be preferred to minimize the likelihood of both false-positive and false-negative results. In addition, controls should be chosen in such a way that, if they were cases, they would be included in the case group; when controls are matched to cases, it is essential to account for matching in the analysis. When appropriate, confounding factors should be controlled for, with particular consideration of race and ethnicity.

Continued advances in SNP maps and in high-throughput genotyping methods will facilitate the analysis of multiple polymorphisms within genes and the analysis of multiple genes within pathways. The effects of polymorphisms are best represented by their haplotypes. Data from multiple polymorphisms within a gene can be combined to create haplotypes, the set of multiple alleles on a single chromosome. A few studies reviewed here reported haplotype associations, although several studies analyzed multiple polymorphisms within a gene, sometimes with inconsistent results. Haplotype analysis can increase the power to detect disease associations because of higher heterozygosity and tighter linkage disequilibrium with disease-causing mutations. In addition, haplotype analysis offers the advantage of not assuming that any of the genotyped polymorphisms is functional; rather, it allows for the possibility of an ungenotyped functional variant to be in linkage disequilibrium with the genotyped polymorphisms.[198] An analysis of data from multiple genes within the same pathway can provide more comprehensive insight into the studied associations. Such an analysis may shed light on the complexities of the many pathways involved in the immune system and AD development, providing hypotheses for future functional studies. Because of concerns over inflated type I error rates in pathway-wide or genome-wide association studies, methods of statistical analysis seeking to obviate this problem are under development.[199] The ability to include haplotype information and data from multiple genes, and to model their interactions, will provide more powerful and more comprehensive assessments of the immune system.

Although the summary risk for developing AD in individuals of each genotype may not be large, AD is such a common disease that even a small increase in risk can translate to a large number of AD cases. Therefore, polymorphisms, even those not strongly associated with AD, should be considered as potentially important public health issues. In addition, it is important to keep in mind that a susceptibility factor in one population may not be a factor in another. There are differences in the prevalence of immune system polymorphisms across populations. In a population where the prevalence of an "at-risk" genotype

in a given polymorphism is very low, the "at-risk" allele or "at-risk" genotype may be too infrequent to assess its associated risk. At a population level, the attributable risk must be small simply because it is an infrequent allele. Finally, the major burden of AD in the population probably results from the complex interaction between many genetic and environmental factors over time. Many harmful substances in the environment first require metabolic activation by Phase I enzymes to their ultimate forms and then the activated forms are detoxified by Phase II enzymes.[200,201] Thus, genetically determined susceptibility to AD may depend on the balance between drug-metabolizing enzyme activity and immune capacity. Further investigations of the combined effects of polymorphisms between immune response genes and drug-metabolizing genes may also help to clarify the influence of genetic variation in the AD development. Consortia and international collaborative studies, which may be a way to maximize study efficacy and overcome the limitations of individual studies, are needed to help further illuminate the complex landscape of AD risk and genetic variations.

The characterization of the genetic factors involved in this common, chronic disorder may provide important clues to its relationship to other diseases, such as asthma and allergic rhinitis, and is ultimately hoped to lead to more effective interventional strategies.

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ELSEVIER

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.
METOHDS: 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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KEY WORDS: Asthma, Cross-sectional Studies, Eczema, Japan, Pregnant Women, Rhinitis.

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

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

Two dust samples were collected from a 1-m^2 area of the bedclothes and flooring for 1 minute using a vacuum cleaner fitted with a collection apparatus. Antigen levels of *Dermatophagoides 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/m^2), ± (5 μg/m^2), + (10–15 μg/m^2), and ++ (>35 μg/m^2). 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)

[a]Antigen levels were semiquantitatively classified with scores of – (<2 μg/m^2), ± (5 μg/m^2), + (10 to 15 μg/m^2), and ++ (>35 μg/m^2).

levels of 10 μg/m^2 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)	

[a]Based 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.
[b]Formaldehyde levels were categorized into 4 groups using cut-off points at the 30th, 60th, and 90th percentile values.
[c]Formaldehyde levels were categorized into 2 groups using a cut-off point at the 90th percentile value.

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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]

	Negative familial allergic history (n = 488)			Positive familial allergic history (n = 510)		
Formaldehyde levels (ppb)	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) (p for trend = 0.06)	2.96 (0.87–10.12)	6/56 (10.7)	1.45 (0.42–4.93) (p for trend = 0.50)	1.63 (0.58–4.57)

[a]Based 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.
[b]Formaldehyde levels were categorized into four groups using cut-off points at the 30th, 60th, and 90th percentile values.
[c]Formaldehyde 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 schoolchildren 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 nondifferential 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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ORIGINAL PAPER **Epidemiology of Allergic Disease**

Tuberculin reactivity and allergic disorders in schoolchildren, Okinawa, Japan

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Clinical and Experimental Allergy

Summary

Background Bacillus Calmette-Guérin (BCG) vaccination triggers a T-helper type 1 response. Whether BCG vaccination and positive tuberculin reactivity are preventive against allergic disorders remains controversial.

Objective The current cross-sectional study investigated the relationship of BCG vaccination and tuberculin reactivity with the prevalence of allergic disorders using data from the Ryukyus Child Health Study (RYUCHS).

Methods Subjects were 5717 schoolchildren aged 8–11 years in Okinawa, Japan. The RYUCHS collected information on symptoms of allergic disorders and potential confounding factors. The outcomes were based on diagnostic criteria from the International Study of Asthma and Allergies in Childhood. Data on BCG vaccination and tuberculin tests were obtained from school records. Allowance was made for grade, sex, sibship size, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

Results No measurable relationship was found between BCG vaccination in infants and the prevalence of allergic disorders. Among 5567 BCG-vaccinated children, positive tuberculin reactivity (induration ⩾10 mm) in the first grade was independently associated with a decreased prevalence of wheeze, asthma, and atopic eczema: the multivariate odds ratios for wheeze, asthma, and atopic eczema were 0.80 (95% confidence interval [CI], 0.67–0.94), 0.78 (95% CI, 0.64–0.95), and 0.77 (95% CI, 0.62–0.95), respectively. The inverse associations were more pronounced in children with a negative parental allergic history than in those with a positive parental allergic history. There was no significant relationship between tuberculin reactivity and allergic rhinoconjunctivitis.

Conclusions The findings suggest that positive tuberculin reactivity may be inversely associated with the prevalence of wheeze, asthma, and atopic eczema, but not allergic rhinoconjunctivitis, especially among Japanese children without a parental allergic history.

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Keywords allergic rhinoconjunctivitis, asthma, atopic eczema, Japanese children, tuberculin reactivity, wheeze

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Introduction

The increase in allergic disorders during the past decades might be to some extent explained by a reduction in bacterial and viral infections and comprehensive vaccination programmes in Japan as well as in Western societies [1]. If an individual has predominantly T-helper type 2 (Th2) cells, the Th2 phenotype interacts with environmental allergens to develop allergic disorders [2]. Infections and immunizations may alter the balance between Th1 and Th2 phenotypes [2].

Bacillus Calmette-Guérin (BCG) vaccination triggers a Th1 response in both healthy adults [3] and newborns [4]. Shirakawa et al. [5] demonstrated a clear relationship among Japanese children between delayed hypersensitivity to tuberculin at the age of 12–13 years and a decreased prevalence of asthma, rhinitis, and eczema, lower levels of total serum IgE and Th2 cytokines, and higher levels of the

Th1 cytokine IFN-γ at the same age. BCG vaccination in early infancy was significantly inversely related to atopy among Guinean children [6] and asthma among Spanish children [7]. However, an ecological study found no relationship between local birth-year immunization rates for tuberculosis and the prevalence of allergic disorders based on the International Study of Asthma and Allergies in Childhood (ISAAC) [8]. A number of epidemiological studies failed to substantiate a clear beneficial association of BCG vaccination or tuberculin reactivity with atopic manifestations [9–19]. Moreover, a study in Turkey showed that tuberculin reactivity in BCG-vaccinated allergic children was stronger than in BCG-vaccinated non-allergic children [20]. Another potential explanation of the previous findings of Shirakawa et al. [5] is an impaired Th1 immunity among atopic individuals [10].

In view of the inconsistency of epidemiological information regarding the relationship of BCG vaccination and tuberculin reactivity with the prevalence of allergic disorders, the current study investigated this issue using data from a part of the Ryukyus Child Health Study (RYUCHS) and school records.

Methods

Study population: the Ryukyus Child Health Study

Naha City and Nago City are two of the 41 municipalities in Okinawa Prefecture. All 35 public elementary schools and 17 junior high schools in Naha City and all 17 public elementary schools and eight junior high schools in Nago City participated in the RYUCHS between September 2004 and January 2005. The purpose of the RYUCHS, a cross-sectional survey, was to investigate the associations between various selected factors and child health problems. A set of two self-administered questionnaires was distributed by teachers to all 38 212 schoolchildren aged 6–15 years. The questionnaires were answered by the parents of the elementary schoolchildren and the junior high school students themselves and/or their parents. When research technicians found missing or illogical data, the teachers sent the questionnaires back to the parents. Finally, 28 885 sets of questionnaires (75.6%) were returned. The ethics committee of the Faculty of Medicine, Fukuoka University, approved the RYUCHS.

Questionnaires

One of the self-administered questionnaires included questions on symptoms of wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months based on the validated ISAAC phase-I questionnaire, which has been reported in detail elsewhere [21–24]. We translated these questions into Japanese by using standard forward–backward translation. Wheeze was considered to be present if respondents answered 'yes' to the written question 'Have you (Has your child) had wheezing or whistling in the chest in the last 12 months?' Those children who responded positively to both the aforementioned question and another question 'Have you (Has your child) ever had asthma?' were considered to have asthma. Atopic eczema was defined as an itchy relapsing skin rash affecting the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes in the past 12 months. Rhinoconjunctivitis was defined as a positive response to both questions 'In the past 12 months, have you (has your child) had a problem with sneezing or a runny or blocked nose, when you (he or she) did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'. The questionnaire also elicited information on grade, sex, sibship size, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis (AR), and paternal and maternal educational level. A paternal or maternal history of asthma, atopic eczema, or AR was defined as positive if the respective parent had any of these allergic disorders since birth.

The other instrument was a validated self-administered brief diet history questionnaire. Data regarding diet were not used in the current study.

Venous blood samples were not taken as part of the RYUCHS; therefore data on total serum IgE and specific IgE were not available in the present study.

Bacillus Calmette-Guérin vaccination and tuberculin reactivity

Japan has been conducting universal BCG vaccination in infants since 1951. Re-vaccination, which had been conducted in Japan since 1954, among tuberculin-negative first grade elementary school and first year junior high school children was discontinued in 2003. The data regarding BCG vaccination status in infants and tuberculin reactivity in the first grade of elementary school were obtained retrospectively from the children's health records at the Naha City Municipal Board of Education. These records were available for children who were in the third, fourth, and fifth elementary school grades at the time of the RYUCHS. Our questionnaires were distributed to 10749 children in the third, fourth, and fifth grade of elementary school in Naha City. Among the 8729 children who took part in the RYUCHS, we obtained data on BCG vaccination and tuberculin reactivity of 6905 individuals. A total of 1188 children were excluded because of missing or illogical data on the factors under investigation. The final analysis included 5717 subjects (53% of eligible children).

School records included information on vaccination status in infants based on a maternal and child health handbook that was provided to all pregnant women by the

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municipality of the domicile although data on the date of BCG vaccination in infants were not available. The immunization was carried out with 10^6 colony-forming units of attenuated bovine *Mycobacterium tuberculosis* (BCG, Tokyo 172 strain, Japan BCG Laboratory, Tokyo, Japan). Among 5717 study subjects, 150 children had not been immunized with BCG in infancy according to school records. Only 44 of the 5567 vaccinated children were revaccinated in the first year of elementary school because of a negative tuberculin response (<10 mm diameter of erythema, but not induration). In this study, tuberculin reactivity was considered positive if the diameter of the induration was 10 mm or greater. The present study was approved by the personal information protection committee of the Government of Naha City.

Statistical analysis

Grade, sex, sibship size, smoking in the household, paternal and maternal history of asthma, atopic eczema, AR, and paternal and maternal educational level were selected *a priori* as potential confounding factors. Grade was classified into three categories (third, fourth, and fifth), sibship size into four (0, 1, 2, and ⩾3), smoking in the household into three categories (never, former, and current), and paternal and maternal educational level into four categories (junior high school, high school, junior college or vocational technical school, and university). Logistic regression analysis was used to estimate crude odds ratios (ORs) and their 95% confidence intervals (CIs). Also, multiple logistic regression analysis was used to control for the potential confounding effects of selected factors. All computations were performed using the SAS software package, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

In the present study, the prevalence values for symptoms of wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months were 12.2%, 8.7%, 7.1%, and 7.6%, respectively.

Table 1 provides the distribution of selected factors among the 5717 subjects. Approximately 60% of the subjects had two or more siblings. About half had at least one current smoker in the household. Many more children had parents with a history of AR than parents with a history of asthma or atopic eczema.

Table 2 presents crude and adjusted ORs and their 95% CIs for allergic disorders in relation to BCG vaccination status in infants. Crude prevalence values for wheeze, asthma, and atopic eczema were approximately 3.0% lower in children immunized with BCG in infancy than in non-BCG-vaccinated children; however, these associations were not statistically significant. Adjustment for grade, sex, sibship size, smoking in the household, paternal and maternal history of asthma, atopic eczema, and AR, and paternal and maternal educational level did not appreciably change these results. No measurable relationship was found between BCG vaccination status in infants and the prevalence of allergic rhinoconjuntivitis.

Table 1. Distribution of selected characteristics in 5717 schoolchildren

Variable	No. (%)
Male sex	2877 (50.3)
Grade	
3	1970 (34.5)
4	1862 (32.6)
5	1885 (33.0)
Sibship size	
0	496 (8.7)
1	2004 (35.1)
2	2143 (37.5)
⩾3	1074 (18.8)
Smoking in household	
Never	2566 (44.9)
Former	493 (8.6)
Current	2658 (46.5)
Paternal history of asthma	424 (7.4)
Paternal history of atopic eczema	148 (2.6)
Paternal history of allergic rhinitis (AR)	1015 (17.8)
Maternal history of asthma	503 (8.8)
Maternal history of atopic eczema	218 (3.8)
Maternal history of AR	1292 (22.6)
Paternal educational level	
Junior high school	399 (7.0)
High school	2448 (42.8)
Junior college or vocational technical school	837 (14.6)
University	2033 (35.6)
Maternal educational level	
Junior high school	256 (4.5)
High school	2402 (42.0)
Junior college or vocational technical school	2558 (44.7)
University	501 (8.8)

Among 5567 BCG-vaccinated children, 2710 (48.7%) in the first grade of elementary school had an induration of 10 mm or greater in diameter. Range was 0–34 mm and the median and 95th percentile values were 9 and 18 mm, respectively (Fig. 1). ORs for allergic disorders in relation to tuberculin reactivity are shown in Table 3. Positive tuberculin reactivity (induration ⩾10 mm) was independently associated with a decreased prevalence of wheeze, asthma, and atopic eczema after allowance for confounding factors under study: the multivariate ORs for wheeze, asthma, and atopic eczema were 0.80 (95% CI, 0.67–0.94), 0.78 (95% CI, 0.64–0.95), and 0.77 (95% CI, 0.62–0.95), respectively. There was no significant relationship between tuberculin reactivity and allergic rhinoconjunctivitis.

When children were divided according to whether there was a negative or positive allergic history in at least one

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Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for allergic disorders in relation to BCG vaccination status in infants in 5717 schoolchildren

	BCG vaccination status	
Variable	Non-vaccinated	Vaccinated
Wheeze		
Prevalence	23/150 (15.3%)	674/5567 (12.1%)
Crude OR (95% CI)	1.00	0.76 (0.49–1.22)
Adjusted OR (95% CI)*	1.00	0.75 (0.48–1.23)
Asthma		
Prevalence	18/150 (12.0%)	481/5567 (8.6%)
Crude OR (95% CI)	1.00	0.69 (0.43–1.18)
Adjusted OR (95% CI)*	1.00	0.68 (0.41–1.17)
Atopic eczema		
Prevalence	15/150 (10.0%)	391/5567 (7.0%)
Crude OR (95% CI)	1.00	0.68 (0.41–1.22)
Adjusted OR (95% CI)*	1.00	0.64 (0.38–1.16)
Allergic rhinoconjunctivitis		
Prevalence	11/150 (7.3%)	422/5567 (7.6%)
Crude OR (95% CI)	1.00	1.04 (0.58–2.05)
Adjusted OR (95% CI)*	1.00	0.93 (0.52–1.86)

*Adjustment for sex, grade, sibship size, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.
BCG, Bacillus Calmette-Guérin.

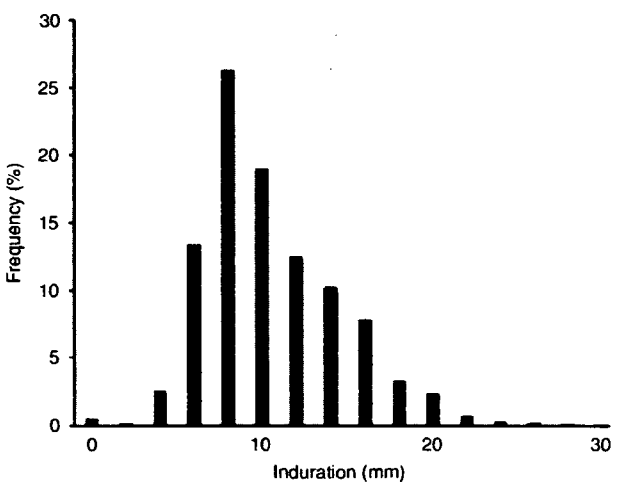

Fig. 1. Distribution of tuberculin reactivity in 5567 BCG-vaccinated first grade students. BCG, Bacillus Calmette-Guérin.

parent, inverse associations of positive tuberculin reactivity with the prevalence of wheeze, asthma, and atopic eczema were more pronounced in children with a negative parental allergic history than in those with a positive parental allergic history in the multivariate model (Table 4). The inverse associations were statistically significant only among children with a negative parental allergic history. No significant interactions were observed in the association of tuberculin reactivity with the

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for allergic disorders in relation to tuberculin reactivity in the first grade in 5567 BCG-vaccinated schoolchildren

	Tuberculin reactivity	
Variable	Negative (induration <10 mm)	Positive (induration ≥10 mm)
Wheeze		
Prevalence	378/2857 (13.2%)	296/2710 (10.9%)
Crude OR (95% CI)	1.00	0.80 (0.68–0.95)
Adjusted OR (95% CI)*	1.00	0.80 (0.67–0.94)
Asthma		
Prevalence	277/2857 (9.7%)	204/2710 (7.5%)
Crude OR (95% CI)	1.00	0.76 (0.63–0.92)
Adjusted OR (95% CI)*	1.00	0.78 (0.64–0.95)
Atopic eczema		
Prevalence	222/2857 (7.8%)	169/2710 (6.2%)
Crude OR (95% CI)	1.00	0.79 (0.64–0.97)
Adjusted OR (95% CI)*	1.00	0.77 (0.62–0.95)
Allergic rhinoconjunctivitis		
Prevalence	223/2857 (7.8%)	199/2710 (7.3%)
Crude OR (95% CI)	1.00	0.94 (0.77–1.14)
Adjusted OR (95% CI)*	1.00	0.96 (0.78–1.18)

*Adjustment for sex, grade, sibship size, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.
BCG, Bacillus Calmette-Guérin.

prevalence of allergic disorders between children with a negative and positive parental allergic history ($P = 0.28$, 0.10, and 0.31 for homogeneity of OR for wheeze, asthma, and atopic eczema, respectively).

Discussion

This study demonstrated that a positive tuberculin response at the age of 6–7 years was significantly inversely associated with the prevalence of wheeze, asthma, and atopic eczema, but not with allergic rhinoconjunctivitis, especially among BCG-vaccinated Japanese children aged 8–11 years without a parental allergic history. There was no statistically significant relationship between BCG vaccination status in infants and the prevalence of any of those allergic disorders. These results were in partial agreement with previous Japanese findings by Shirakawa et al. [5] and epidemiological studies showing no association between BCG vaccination and atopy [9, 10, 16–18], but at variance with previous research that found no statistically significant relationship between tuberculin reactivity and allergy [9, 11–15, 17, 19].

Our results regarding a significant inverse association between tuberculin reactivity and wheeze, asthma, and atopic eczema may be explained by the BCG strain used in Japan. A laboratory study in mice showed that

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Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for allergic disorders in relation to tuberculin reactivity in the first grade in 5567 BCG-vaccinated schoolchildren with a negative or positive parental allergic history

	Adjusted OR (95% CI)*	
Variable	Negative tuberculin reactivity (induration <10 mm)	Positive tuberculin reactivity (induration ≥10 mm)
Wheeze		
Negative parental allergic history (n = 3187)	1.00	0.71 (0.54–0.93)
Positive parental allergic history (n = 2380)	1.00	0.87 (0.70–1.08)
Asthma		
Negative parental allergic history (n = 3187)	1.00	0.63 (0.45–0.88)
Positive parental allergic history (n = 2380)	1.00	0.90 (0.70–1.15)
Atopic eczema		
Negative parental allergic history (n = 3187)	1.00	0.71 (0.50–0.99)
Positive parental allergic history (n = 2380)	1.00	0.80 (0.61–1.06)
Allergic rhinoconjunctivitis		
Negative parental allergic history (n = 3187)	1.00	0.75 (0.52–1.07)
Positive parental allergic history (n = 2380)	1.00	1.09 (0.84–1.40)

*Adjustment for sex, grade, sibship size, smoking in the household, and paternal and maternal educational level.
BCG, Bacillus Calmette-Guérin.

methacholine sensitivity and concentrations of IL-5 and IL-10 in the supernatant of cultured splenocytes were significantly lower only in the group treated with the Tokyo 172 strain, but not in those treated with the other three strains of BCG [25]. Moreover, a recent laboratory investigation demonstrated that IL-21-induced Bε cell apoptosis is the mechanism responsible for the BCG-mediated suppression of IgE production [26]. Alternatively, the inverse associations in our study might be ascribed to asymptomatic infection by environmental non-tuberculous mycobacteria, but data on environmental mycobacterial exposure were not available in the present study. However, a cross-sectional study in Sweden showed a higher, rather than a lower, prevalence of cutaneous reactivity to atypical mycobacteria in allergic than in non-allergic children whereas there was a tendency towards a lower prevalence of strongly positive skin reactions to mycobacteria in allergic than in non-allergic children [10]. A decreased ability of atopic patients to mount strong Th1 cell-mediated immune responses might result in decreased capacity to avert infection by atypical mycobacteria [10]. This assumption regarding altered immune responsiveness in atopic individuals is not likely to explain the more evident inverse associations in children without a parental allergic history than in those with a parental allergic history in the present study, however. A review proposed that an increase of Th2 cytokine expression, the so-called Th2 paradigm, is related to atopy and inception of asthma whereas Th1 activation would account at least in part for asthma symptoms [27].

We observed no relationship between tuberculin reactivity and the prevalence of allergic rhinoconjunctivitis. Different mechanisms might be involved in the manifestation of asthma and atopic eczema than in allergic rhinoconjunctivitis regarding the beneficial effects of BCG vaccination. A significant inverse association between a positive tuberculin response and rhinitis was found among Japanese adolescents, however [7].

The current study had several methodological strengths. Study subjects were homogenous with respect to age and residential background and the prevalence of allergic disorders was assessed by validated ISAAC-based questions. We were able to incorporate extensive data on potential confounding factors. However, no allowance was made for infectious history, immunization other than BCG, or external factors such as air pollution and toxic chemicals. The sample size was sufficient to adequately examine the associations of tuberculin reactivity with allergic disorders. However, the very low proportion of non-BCG-vaccinated children might not have allowed us to detect true inverse associations with BCG vaccination in infants.

Of the 10749 public elementary schoolchildren in the third, fourth, and fifth grade in Naha City, 5717 (53%) were included in this investigation. With regard to the 2020 non-participants in the RYUCHS, no information on factors under study was available. It is difficult to know whether our study subjects represented a different group than those not studied in terms of exposures, outcomes, or confounders under study. We compared the answers given by 3012 participants who were excluded because of incomplete data with answers by the 5717 study subjects who completed all data. Compared with the 3012 participants, the 5717 study subjects were less likely to have no siblings, fathers with a history of atopic eczema and AR and mothers with a history of asthma, atopic eczema, and AR and were more likely to be male and young and have family members who had never smoked, fathers with a low educational level, and mothers with a high educational level (data not shown). There was no statistically significant difference between the excluded participants and study subjects regarding the prevalence of wheeze, asthma, atopic eczema, and allergic rhinoconjunctivitis, a paternal history of asthma, and tuberculin reactivity.

Okinawa Prefecture is an island located in the southernmost area in Japan and has a subtropical climate. The distribution of various environmental factors in Okinawa

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is likely to be different from that in the mainland of Japan. In fact, the prevalence of allergic disorders in the current study was quite different from that in the mainland of Japan. According to a cross-sectional study among Japanese adolescents in Sùita City in an urban area of the mainland, the prevalence values for symptoms of wheeze, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months were 6.7%, 14.5%, and 23.9%, respectively, by using the ISAAC criteria [28]. Therefore, we should be cautious in generalizing the present observations.

BCG vaccination and tuberculin tests were performed by many different persons. This type of exposure misclassification would be random with respect to outcomes under investigation. The consequence would bias the estimations of the association towards the null.

In conclusion, the current results partially corroborate a previous Japanese report, which showed an inverse association between a positive tuberculin response and some allergic parameters. However, both the current and previous studies do not necessarily indicate a causal relationship between tuberculin reactivity and allergy. Prospective studies are necessary to answer the question of whether positive tuberculin reactivity caused by BCG vaccination is protective against allergic disorders, taking into consideration additional environmental factors together with genetic factors.

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