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

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

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.

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.

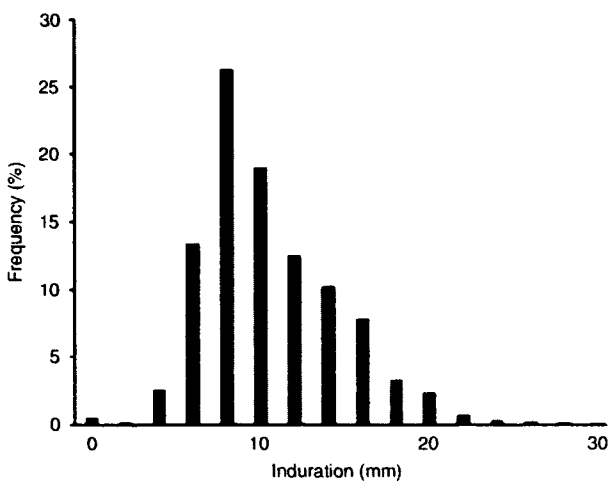

Fig. 1. Distribution of tuberculin reactivity in 5567 BCG-vaccinated first grade students. BCG, Bacillus Calmette-Guérin.

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 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

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

Variable	Adjusted OR (95% CI)*	
	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

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 Sûita 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.

Acknowledgements

This study was supported by Health and Labour Sciences Research Grants, Research on Allergic Disease and Immunology from the Ministry of Health, Labour, and Welfare, Japan.

The authors would like to acknowledge the Naha City Municipal Board of Education and Nago City Municipal Board of Education for their valuable support; Hatsuko Kadekaru, ME, Research Project for Longevity Science, University of the Ryukyus, and Ayako Yoshida, ME, Department of Welfare, Faculty of Health and Welfare, Seinan Jo Gakuin University for helpful discussions; the teaching staff at participating schools for help with data collection; Mr Takuya Ohgushi, Mr Takayuki Okamoto, Ms Michiyo Kohtake, Ms Takako Kanki, Ms Mamiko Miyano, and Ms Yumi Arimitsu for their assistance; and all of the children and parents participating in the RYUCHS.

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アレルギー疾患の発症関連要因

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近年，日本を含め先進国では，アレルギー疾患が急激に増加している．一方で先進国と発展途上国との間には有症率に差が認められ，また，同一国内においても有症率の地域差が観察される．これらの所見を，単に遺伝的要因のみで説明することは難しい．生活環境や食習慣をはじめとした生活習慣の変化や地域差が，アレルギー疾患発症に関与している可能性が高い．1989年にStrachan[1]により，衛生環境の改善による小児期の感染機会の減少がアレルギー疾患発症と関連しているのかもしれないという衛生仮説が提唱された．この衛生仮説が提示されて以降，アレルギー疾患の原因を解明し，予防方法を確立するために，多くの疫学研究が実施されてきた．しかしながらその結果は一致しておらず，今日においても未だ確たる結論が得られていない．

以前，われわれは2000年1月以降2006年8月までに公表された環境要因とアレルギー疾患との関連に関する疫学研究を対象に，系統的なレビューを実施した[2]．本稿では以前のレビューの結果に加えて，レビュー執筆以降に公表された最新の疫学研究結果を追加し，アレルギー疾患(喘鳴，喘息，アトピー性皮膚炎，アレルギー性鼻炎)との関連における環境要因の科学的根拠についてまとめる．

環境要因とアレルギー疾患との関連に関する疫学研究

1. 検討する論文の抽出

PubMedを活用し，「(asthma OR wheeze OR "atopic dermatitis" OR "atopic eczema" OR "allergic rhinitis") AND (risk OR prevalence OR preventive OR protective) AND (association OR relationship) AND human AND (cross-sectional OR case-control OR prospective OR cohort OR intervention) NOT polymorphism」というキーワードを用いて検索を行った．以前のレビューでは1,093の論文が検出され，これらの論文のタイトルと抄録内容を吟味し，① 原著論文であること，② 分析疫学研究であること，③ 喘鳴，喘息，アトピー性皮膚炎，アレルギー性鼻炎を結果因子としていること，の3つの基準に合致した263の論文を検討した．今回，以前のレビュー以降，2007年10月20日までの期間でPubMedを活用し，同じ条件で検索したところ，233編の論文が検出され，そのうちの42編の論文を追加で検討することとした[3~44]．結果の解釈では，① 関連の強さのp値が<0.05，または② 傾向性のp値が<0.05であるときに，有意な関連があるとみなした．**表**中には，関連の向き(正の関連がある場合：↑，負の関連がある場合：↓，関連がない場合：N)と，各アレルギー疾患ごとのエビデンスの総数，および括弧内にはコホート研究，症例対照研究，

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横断研究のそれぞれの数を示した.

2. 食事要因以外の環境要因とアレルギー疾患

今回のレビューでは環境要因として,喫煙(能動喫煙・受動喫煙・妊娠中の喫煙),体重(肥満・やせ・出生時体重),ペット飼育,ハウスダスト(ダニ抗原・エンドトキシン),室内の湿度,ワクチン接種(DTP, DT, D, T, P, ポリオ, BCG),抗生剤の使用,呼吸器感染症に着目して,結果をまとめた(**表1**).

1) 喫煙との関連

喫煙とアレルギー疾患との関連については,比較的多くの論文において検討されていた.能動喫煙との関連に関して39の結果が公表されており,このうち21の結果では,喘鳴や喘息との間に,統計学的に有意な正の関連が見られた.一方,残りの16の結果ではアレルギー疾患と統計学的に有意な関連を認めず,2つの結果では,喘息やアレルギー性鼻炎との間に統計学的に有意な負の関連を認めた.受動喫煙に関しては72の結果があり,このうち21の結果でアレルギー疾患と有意な正の関連を認め,残りの51の結果では統計学的に有意な関連を認めなかった.妊娠中の母親の喫煙との関連については29の結果があり,このうち7つで正の関連,残りの22の結果では関連を認めなかった.

多くの疫学研究においては,喫煙状況に関する情報収集は,自記式の質問調査票やインタビュー形式を採用しているため,喫煙状況に関して誤分類が起こりやすいと考えられる.煙草煙曝露に関して客観的な指標(唾液や血清バイオマーカーなど)を用いた研究が望まれる.負の関連が一部の結果で認められるが,healthy smoker effect,つまり,アレルギーであるが故に,煙草を控えている結果なのかもしれない.喫煙とアレルギー疾患との関連について結論を得るには,さらなる研究が必要である.

2) 体重(肥満・やせ)との関連

肥満とアレルギー疾患との関連に関して,76の結果が公表されている.このうち44の結果で肥満とアレルギー疾患との間に正の関連を認め,

表1 環境要因とアレルギー性疾患との関連

因子	関連	喘鳴	喘息	アトピー性皮膚炎	アレルギー性鼻炎(花粉症含)
能動喫煙	↑	7(1, 0, 6)	14(4, 1, 9)	—	—
	↓	—	1(0, 0, 1)	—	1(0, 0, 1)
	N	1(1, 0, 0)	10(1, 1, 8)	2(0, 0, 2)	3(0, 0, 3)
受動喫煙	↑	6(1, 0, 5)	11(2, 3, 6)	—	4(1, 0, 3)
	↓	—	—	—	—
	N	10(4, 0, 6)	25(8, 2, 15)	8(1, 3, 4)	8(1, 0, 7)
妊娠中の喫煙	↑	2(2, 0, 0)	5(1, 2, 2)	—	—
	↓	—	—	—	—
	N	7(6, 0, 1)	7(4, 1, 2)	5(3, 0, 2)	3(1, 0, 2)
肥満	↑	12(1, 0, 11)	30(11, 3, 16)	—	2(0, 0, 2)
	↓	—	—	—	—
	N	7(2, 0, 5)	16(3, 2, 11)	4(2, 1, 1)	5(2, 0, 3)
やせ	↑	1(0, 0, 1)	3(1, 0, 2)	—	1(1, 0, 0)
	↓	1(0, 0, 1)	—	—	—
	N	2(0, 0, 2)	9(2, 2, 5)	—	—
低体重出生	↑	2(2, 0, 0)	3(3, 0, 0)	—	—
	↓	—	—	—	—
	N	5(4, 0, 1)	10(9, 0, 1)	4(3, 0, 1)	3(2, 0, 1)
ペットの飼育	↑	2(1, 0, 1)	5(0, 2, 3)	—	2(0, 0, 2)
	↓	4(3, 0, 1)	5(1, 1, 3)	5(4, 0, 1)	2(0, 0, 2)
	N	14(7, 0, 7)	14(4, 1, 9)	9(3, 1, 5)	4(0, 0, 4)
ハウスダスト(ダニ抗原)	↑	1(1, 0, 0)	2(1, 1, 0)	—	—
	↓	—	—	—	—
	N	8(3, 3, 2)	6(4, 2, 0)	3(1, 0, 2)	3(1, 0, 2)
ハウスダスト(エンドトキシン)	↑	6(5, 0, 1)	—	—	—
	↓	—	1(1, 0, 0)	1(1, 0, 0)	1(1, 0, 0)
	N	6(4, 1, 1)	2(0, 1, 1)	3(3, 0, 0)	2(1, 0, 1)
室内の湿度	↑	9(3, 2, 4)	5(0, 1, 4)	5(1, 1, 3)	4(0, 0, 4)
	↓	—	—	—	—
	N	6(2, 0, 4)	7(2, 1, 4)	9(2, 4, 3)	4(1, 0, 3)
DTP, DT, D, T, Pワクチン	↑	—	—	—	—
	↓	—	—	1(0, 1, 0)	—
	N	1(0, 0, 1)	4(2, 0, 2)	—	1(0, 0, 1)
ポリオワクチン	↑	—	—	—	—
	↓	—	—	1(0, 1, 0)	—
	N	1(0, 0, 1)	4(2, 1, 1)	—	—
BCG	↑	—	—	—	—
	↓	1(1, 0, 0)	—	—	—
	N	2(0, 0, 2)	3(1, 0, 2)	—	—
抗生剤の使用	↑	3(1, 0, 2)	8(6, 0, 2)	1(0, 0, 1)	2(1, 0, 1)
	↓	—	—	—	—
	N	2(2, 0, 0)	8(6, 1, 1)	6(3, 2, 1)	14(10, 3, 1)
呼吸器感染症	↑	5(3, 0, 2)	10(6, 0, 4)	—	1(1, 0, 0)
	↓	—	—	—	—
	N	4(3, 0, 1)	4(3, 0, 1)	4(2, 1, 1)	2(1, 0, 1)

↑:有意な正の関連あり ↓:有意な負の関連あり N:統計学的に関連なし
表中の数字は,総文献数(コホート研究数,症例対照研究数,横断研究数)を表す

表2 食事要因とアレルギー性疾患との関連

因子	関連	喘鳴	喘息	アトピー性皮膚炎	アレルギー性鼻炎(花粉症含)
野菜・果物	↑	—	1(0, 0, 1)	1(0, 1, 0)	—
	↓	4(0, 0, 4)	3(0, 1, 2)	—	1(0, 0, 1)
	N	6(0, 0, 6)	5(0, 0, 5)	2(0, 1, 1)	4(0, 0, 4)
魚	↑	—	—	—	—
	↓	1(0, 0, 1)	1(0, 0, 1)	—	1(0, 0, 1)
	N	3(0, 0, 3)	1(0, 1, 0)	—	2(0, 0, 2)
肉	↑	—	—	—	—
	↓	—	1(0, 0, 1)	—	1(0, 0, 1)
	N	3(0, 0, 3)	3(0, 2, 1)	—	2(0, 0, 2)
乳製品	↑	—	—	—	—
	↓	2(2, 0, 0)	8(2, 1, 5)	1(0, 0, 1)	2(0, 0, 2)
	N	7(1, 0, 6)	10(2, 3, 5)	4(0, 0, 4)	6(0, 0, 6)
アルコール	↑	—	—	—	—
	↓	—	—	—	—
	N	1(0, 0, 1)	2(1, 0, 1)	—	—
ビタミンC	↑	1(1, 0, 0)	—	1(1, 0, 0)	—
	↓	—	1(0, 1, 0)	—	—
	N	3(1, 0, 2)	3(0, 1, 2)	—	—
n-3系脂肪酸	↑	1(0, 0, 1)	2(0, 1, 1)	—	—
	↓	—	—	1(0, 0, 1)	2(0, 1, 1)
	N	2(0, 2, 0)	7(0, 4, 3)	—	4(0, 0, 4)
n-6系脂肪酸	↑	—	—	—	—
	↓	—	—	—	—
	N	—	3(0, 2, 1)	2(0, 0, 2)	5(0, 0, 5)
母乳	↑	—	4(3, 1, 0)	4(2, 0, 2)	—
	↓	5(4, 0, 1)	5(4, 0, 1)	1(1, 0, 0)	1(0, 0, 1)
	N	6(3, 0, 3)	7(4, 0, 3)	10(6, 1, 3)	6(2, 0, 4)

↑：有意な正の関連あり
↓：有意な負の関連あり
N：統計学的に関連なし
表中の数字は，総文献数(コホート研究数，症例対照研究数，横断研究数)を表す

残りの32の結果では統計学的に有意な関連を認めなかった．負の関連を認めた結果は存在しなかった．やせとの関連に関しては，17の結果が存在し，このうち5つで正の関連，1つで負の関連，残りの11では関連を認めなかった．現段階においては，肥満およびやせとアレルギー疾患との関連については研究数が未だ不十分であるので，結論を導くことはできない．

3) 室内の湿度との関連

室内の湿度とアレルギー疾患との関連に関するこれまでの疫学研究では，室内の湿度の定義は一定していない．例えば室内でのカビの発生，窓の結露，室内での水漏れなど，研究によって様々であった．現段階で，室内の湿度とアレルギー疾患との関連に関する49の結果が公表されていた．このうち23の結果では正の関連を認め，残りの26の結果では関連を認めなかった．負の関連を示した結果は存在しなかった．

4) ワクチン接種との関連

今回，DTP，DT，D，T，P，ポリオおよびBCGワクチン接種との関連に関する結果をまとめた．ワクチン接種とアレルギー疾患とに関するエビデンスは非常に少なく，19の結果のみであった．ワクチン接種とアレルギー疾患との間に正の関連を認めた結果は存在しなかった．16の結果では関連を認めず，負の関連を認めた結果は3つであった．

5) 抗生剤の使用との関連

抗生剤の使用とアレルギー疾患との関連に関して，44の結果が公表されている．このうち14の結果では正の関連，残りの30の結果では，統計学的に有意な関連を認めなかった．負の関連を示した結果は存在しなかった．現段階では研究数が少なく，抗生剤の使用とアレルギー疾患との関連について結論を出すことはできない．

3. 食事要因とアレルギー疾患

食事要因とアレルギー性疾患との関連に関する結果を**表2**にまとめた．喘鳴や喘息に比較すると，アトピー性皮膚炎やアレルギー性鼻炎を結果因子とした疫学研究は少なかった．

野菜や果物の摂取とアレルギー疾患とに関するエビデンスは27存在した．このうち2つの結果では正の関連を認め，8つの結果では負の関連，残りの17の結果は，統計学的に有意な関連を認めなかった．魚や肉の摂取とアレルギー疾患とに関する結果は非常に少なく，それぞれ9と10のみ存在した．またそのほとんどで，統計学的に有意な関連を認めなかった．乳製品摂取との関連については，40の結果が存在した．このうち負の関連を認めたのは13であった．残りの27の結果では関連を認めなかった．これらの食事要因とア

レルギー疾患とに関するエビデンスは非常に少なく，現段階で結論を導くことはできない．

母乳摂取とアレルギー疾患との関連に関しては，49の結果が存在した．このうち，喘息およびアトピー性皮膚炎との間に正の関連を認めた結果が8，喘鳴，喘息，アトピー性皮膚炎およびアレルギー性鼻炎との間に負の関連を認めた結果は12であった．一方，母乳摂取と各アレルギー疾患との間に統計学的に有意な関連を認めなかったのが29であった．母乳摂取とアレルギー疾患との関連に関する結果は一致しておらず，また，研究数が未だ十分とは言えないため，今後のさらなる研究が望まれる．

まとめ

今回，以前にわれわれが実施したレビューに最新の疫学研究結果を加え，環境要因とアレルギー疾患との関連に関する現時点での科学的根拠についてまとめた．様々な環境要因や食事要因とアレルギー疾患との関連について検討されていたが，喘鳴，喘息，アトピー性皮膚炎およびアレルギー性鼻炎のいずれのアレルギー疾患に関しても，研究数が不十分な上，それらの研究結果は一致しておらず，現段階で明確な結論を導くことはできない．疾患ごとの研究数に着目すると，喘鳴および喘息に関する疫学研究に比較し，アトピー性皮膚炎やアレルギー性鼻炎に関する疫学研究は非常に少ない状況であった．

今回のわれわれのレビュー結果を解釈する際には，以下の点について注意が必要である．まず第一に，今回のレビューでは英語の論文のみに限定して検索した．このため，日本語をはじめ，他の言語で報告された結果は考慮できていない．第二に，アレルギー疾患の定義が研究によって異なっている．例えば妥当性の検証された国際的疫学診断基準(ISAAC：the International Study of Asthma and Allergies in Childhood や ECRHS：the European Community Respiratory Health Survey)を活用して疾患を定義している研究や，医師の診断を採用している論文，また単に，質問調査票で医師の診断の有無のみを判断基準にしている論文等，様々な定義が用いられている．本来，異なる定義を用いて実施された研究結果を，同等に比較することは好ましくない．第三として，対象者の年齢が研究によってまちまちである．アレルギーのリスク要因，予防要因は年齢によって異なっているかもしれない．情報収集の方法については，小児を対象とした研究の多くは，保護者に対して質問調査票やインタビューを実施している．成人を対象とした本人から直接得る情報とは，情報の質が異なっているかもしれない．第四として，今回のレビューで検討した論文には，横断研究が比較的多い．横断研究では，原因と結果の時間的前後関係が不明であるため，因果の逆転が生じている可能性がある．すなわち，既にアレルギー疾患に罹患しているために，生活習慣を変化させているかもしれない．最後に，今回検討した論文はたった1つの検索式で系統的に収集したものであり，多数の考慮できなかった疫学研究も存在することに注意すべきである．

環境要因および食事要因とアレルギー疾患との関連についての疫学論文は未だ十分でなく，また，その結果も一致していないため，現段階において明確な結論を述べることはできない．さらに日本をはじめアジア諸国において実施された研究はほとんどない．環境要因や食事要因は，人種や国，地域によって大きく異なっているため，欧米諸国から公表された疫学研究結果を，直接われわれ日本人にあてはめることは適切でない．今後，日本人を対象とした質の高い研究を実施していく必要がある．

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