

Effect of lifestyle on levels of specific IgE antibodies

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Specific IgE antibodies against cobalt-conjugated human serum albumin (Co-HSA) were determined in serum samples from 706 hard metal workers who responded to a questionnaire on 17 physical and mental health practices. Hard metal (an alloy of cobalt) exposure resulted in significant ($P < 0.05$) increases in Co-HSA RAST indices in male subjects. In contrast, no factor concerning health practices made an independent contribution to elevation or suppression of specific IgE levels against cobalt. Although total IgE level was found to be significantly ($P < 0.01$) modulated by the cumulative health practice index (HPIA: Health Practice Index in Allergic reaction), which was extracted by MANOVA analysis while controlling for sex, age, and environmental factors, no significant association was found between HPIA and specific IgE level against cobalt. Multiple logistic analysis also revealed that health practices and hard metal exposure had a significant relative risk (> 2.3 ; $P < 0.05$) of elevating Co-HSA RAST index when the total IgE level was more than 400 IU/ml. Thus, a *healthy* lifestyle as well as discouragement of occupational exposure may be of benefit in reducing allergic disorders for persons with high IgE levels.

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Our previous paper (25) demonstrated that while sex, age, and occupational exposure levels are controlled for, lifestyle has a cumulative influence on elevating or suppressing total IgE level. To evaluate lifestyle effect on total IgE levels, we compiled a cumulative index, HPIA (Health Practice Index in Allergic reaction), which was composed of eight health practices identified by MANOVA analysis (27). This was reinforced by recent epidemiologic studies in which some health factors, including smoking (3, 4, 5, 7, 11–16, 26), alcohol drinking (7, 14, 25), and diet (21, 28), that are included in the HPIA have made an independent contribution to the modulation of total IgE levels.

In our series of papers (23–26), we found that the higher the total IgE level, the higher the specific IgE level that might be responsible for the patient's type I allergy. However, the development, disappearance, remission, and/or exacerbation of such allergic diseases are mainly dependent on sensitization levels, that is, specific IgE levels, not on total IgE levels (23, 26).

A person's risk of sensitization depends upon the degree of exposure to potential allergens. Studies of occupational allergy demonstrate that the greater the exposure, the higher the prevalence of sensitization (25). Similar relationships are documented in asso-

ciation with enzyme detergents (19), snow crabs (6), coffee beans (32), ispaghula (32), laboratory animals (31), and tetrachlorophthalic anhydride (TCPA) (30). Most workers sensitized to those haptens were smokers (6, 19, 30, 32). However, stress (20) and nutrition (22) have also been associated with specific antibodies against some allergens in animal experiments. These findings should focus our interest on the relation between individual health practices, occupational exposure, and specific IgE levels.

The purpose of this study was therefore to determine whether the comprehensive lifestyles responsible for total IgE levels also play a significant role in the modulation of specific IgE against cobalt while some confounding variables were controlled for. This approach offers further insights into the dynamics of the relationship between total and specific IgE levels, and lifestyles, and enables us to offer further protection from allergic disorders.

Material and methods

Subjects

A sample population (706 workers) was chosen from a hard metal plant, although it was confined to workers aged 18 years and older, because 1) this popu-

lation is typical of Japanese plant workers, and 2) it enables us to quantitate an individual dose-response relationship for cobalt exposure. Details of the subject criteria were described in detail in our previous paper (18, 23). Hence 570 male as well as 136 female workers were available as nonatopic subjects in the factory.

Environmental studies

These studies were described in detail in our series of reports (18, 23). Briefly, total dust and mist in the breathing zones were collected several times by means of a dust-sampling pump for about 6 h, and cobalt in the samplers was detected by atomic absorption spectrophotometry (Hitachi, Japan) with sensitivity at 0.5 ppm (18). Each worker was interviewed regarding his or her work status, and those engaged in handling hard metal were identified as having a positive history of exposure.

Serologic analysis

Serum samples were collected from all the subjects and frozen at -80°C until the tests were done. Specific RAST with cobalt-conjugated human serum albumin (Co-HSA) was done in duplicate in the same run according to our previous method (24). The RAST scores were calculated by dividing the cpm (count per min) obtained from test serum samples incubated with Co-HSA by the cpm obtained from test serum incubated with HSA (Co-HSA RAST / HSA RAST).

Questionnaire and data analysis

We used a questionnaire including both physical and mental health (25): 17 habits were included in the questionnaire. These covered eating habits (regularity of meals, salt consumption, nutritional balance, eating breakfast, and snacking), mental qualities (enjoying hobbies, feeling busy, subjective mental stress, life satisfaction), physical qualities (exercise, physical condition compared with that of 6 months ago), habit-forming tastes (smoking status, alcohol consumption, and tea or coffee consumption), and basic living pattern (working time, regularity of daily life, sleeping time). Subjects responded to the questionnaire during medical examinations, and the data were analyzed by Osaka University's ACOS-6 NEC computer system with the SPSSX (Statistic Package for Social Sciences extension, version 2.2) program (27). The incomplete answers (seven subjects) were excluded. The basic structure as well as the validity and reliability of this questionnaire was described in our previous paper (25).

Results

Distribution of Co-HSA RAST index

The distribution of the Co-HSA RAST index was certainly left skew, with a mean value of 1.26 ± 0.16 . Male subjects had a higher (1.26 ± 0.12) mean RAST index than that (1.16 ± 0.11) of female (Fig. 1A). A score of more than 1.74, which was considered to be positive on the basis of Student's *t* distribution (mean + 3 SD; $P < 0.01$), was found in the nine men and one woman who had been diagnosed as having occupational asthma caused by hard metal exposure.

Exposure effect of hard metal on Co-HSA RAST index

Cobalt exposure resulted in significant ($P < 0.05$) increases in Co-HSA RAST indices in the male subjects: the mean index was 1.16 ± 0.13 in nonexposed subjects and 1.37 ± 0.13 in exposed subjects, while there was no difference in the women despite gradual increases in the exposed group (Fig. 1B). This difference cannot be explained by the differences in

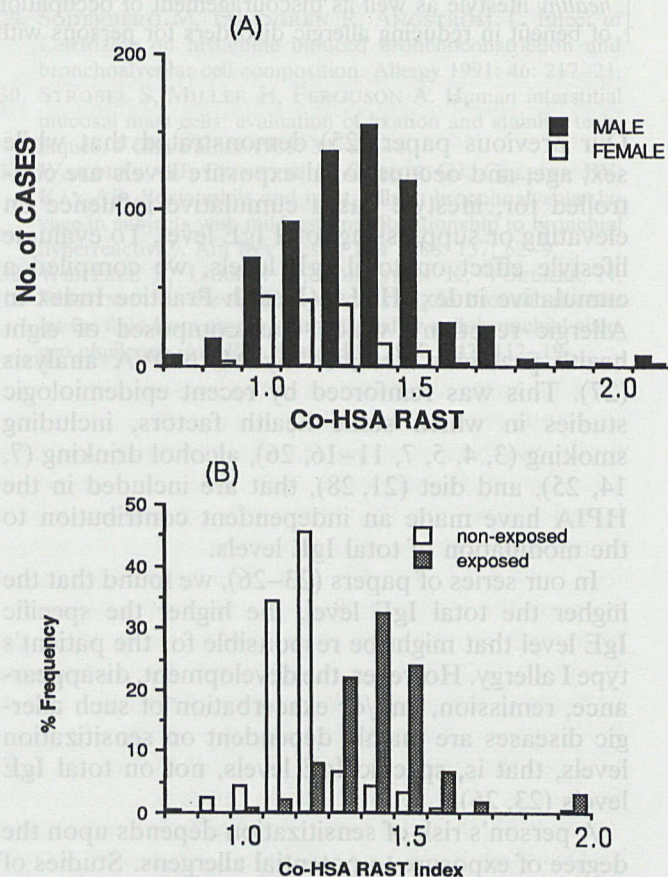


Fig. 1. (A) Frequency distribution of Co-HSA RAST index by sex and (B) by exposure status in male subjects. Specific RAST was determined by our previously described method.

ages or dust exposure doses (Table 1). Furthermore, the specific RAST indices against Co-HSA displayed certain correlations not only with the intensity of cobalt exposure ($r=0.488$; $P<0.001$), but also with $\log[\text{total exposure doses}]$ ($r=0.578$; $P<0.001$).

Effect of lifestyle on Co-HSA RAST index

Questionnaire items each had 2–6 possible answers, each of which was categorized as *good* or *poor* according to our criteria (1). In the results of serum specific IgE against cobalt, no factor provided a significant difference between the *good* and *poor* categories (Table 2). According to total IgE levels, five factors tending to increase IgE (enjoying hobbies, working time, regularity of eating, sleeping patterns, and subjective mental stress) and three tending to decrease IgE (feeling busy, alcohol consumption, and smoking habits) were extracted from 18 items by MANOVA analysis (27) after holding confounders constant. Furthermore, to augment the cumulative effect of these two types of factors, we constructed

Table 1. Risk of elevated specific IgE against cobalt (Co-HSA RAST index) related to health practices, HPIA categories, sex, age, and hard metal exposure (multiple logistic analysis). The cutoff points of Co-HSA RAST index for high-risk status were determined on the basis of more than 2 SD on Student's *t* test

		Relative risk [†]	
		Total IgE level (IU/ml)	
	High risk	> 400 IU/ml	5–400 IU/ml
Regularity of daily life	irregular	2.6 (1.4–4.0) ^{††}	1.1 (0.4–1.9)
Enjoying hobbies	no	0.9 (0.2–1.1)	1.0 (0.4–2.0)
Feeling busy	yes	0.9 (0.3–1.3)	0.9 (0.4–1.5)
Physical exercise	< 1/wk	1.4 (0.5–2.5)	1.0 (0.4–2.0)
Alcohol consumption	every day	1.3 (0.4–3.3)	1.1 (0.2–1.3)
Smoking habits	Present	1.6 (0.5–2.2)	1.2 (0.4–2.0)
Sleeping pattern	< 6, > 9 h	1.4 (0.5–2.4)	1.3 (0.4–2.5)
Regularity of eating	no	1.0 (0.4–2.2)	1.0 (0.3–1.4)
Nutritional balance	poor	1.6 (0.4–4.0)	1.6 (0.4–3.8)
Eating breakfast	not very day	1.0 (0.4–2.2)	1.0 (0.4–2.0)
Coffee, tea consumption	> 5 cups/day	0.8 (0.2–2.5)	0.9 (0.3–2.9)
Working time	> 10 h	1.3 (0.4–4.0)	1.3 (0.4–3.0)
Subjective mental stress	strong	1.3 (0.4–3.0)	1.1 (0.3–2.2)
Conditional changes	worse	1.0 (0.4–1.9)	1.1 (0.3–2.2)
Life satisfaction	little	0.9 (0.2–1.4)	1.0 (0.4–2.3)
Snacking	every day	1.0 (0.5–2.3)	0.8 (0.2–2.2)
Salt consumption	poor control	1.0 (0.3–2.0)	0.8 (0.3–2.0)
HPIA	high	1.0	1.0
	moderate	1.8 (0.8–3.3)	1.6 (0.6–3.3)
	low	2.3 (1.9–3.8)*	1.8 (1.0–4.5)
Sex	male	1.2 (0.5–3.3)	1.0 (0.3–3.3)
Age	> 35 yr	1.1 (0.4–2.8)	1.1 (0.3–3.0)
Hard metal exposure	yes	3.8 (2.1–5.5)**	3.0 (2.2–5.6)*
	high dose	2.3 (1.0–4.4)*	1.3 (0.6–2.0)

[†] Odds ratio between low-risk and high-risk; ^{††} 95% confidence limits.

* $P<0.05$; ** $P<0.01$.

an HPIA with each of eight factors being recorded as a dichotomized value and scored as 1 (*poor*) or 0 (*good*): every respondent received an HPIA (from 0 to 8) based on the following formula: HPIA = number of DNFs (downward normalizing factors) + [5 – number of UNFs (upward normalizing factors)] (25). A definite ($P<0.05$) trend for the total serum IgE to increase with scores of modified HPIA was found within age strata defined, irrespective of hard metal exposure. However, a definite but nonsignificant ($P=0.07$) combination effect was found on the Co-HSA RAST index.

Higher specific IgE levels often predict the subsequent development of type I allergic response (1). The next step was thus to examine the role that *unhealthy* categories of each lifestyle play in determining high risk of elevated RAST indices on the basis of higher or normal total IgE level by multiple logistic analysis (25). Seventeen health practices as well as three confounders (sex, age, cobalt exposure) were dichotomized and scored as 0 (low risk) or 1 (high risk). The cutoff points of specific IgE levels for high-risk status (RAST index score > 1.58) were determined on the basis of 2 SD above mean levels of Co-HSA RAST index (Fig. 1B).

As shown in Table 1, relative risks (RR) ranged from 1.6 to 3.1, and cobalt exposure had the highest contribution to risk of elevated specific IgE against cobalt. However, from four to six health practices had a substantial ($RR>1.0$), but nonsignificant, association with risk of elevated IgE level when total IgE was within normal range (5–400 IU/ml). Age and sex may not exert effects independently ($RR=1.1$) on development of both risk statuses in the model used for the present study.

In contrast, when total IgE level was more than 400 IU/ml, two developments, 1) a strong increase in risk status associated with combinations of health practices (UNFs, DNFs, and HPIA), and 2) a dramatic enhancement of RR among HPIA categories, confirm that health practices together have a cumulative influence on IgE levels, while each alone makes no independent contribution to their determination. These results were quite similar to those obtained from univariate analyses.

Discussion

In epidemiologic studies, the host of environmental factors that account for the development of concordant allergy in persons remain unknown (1). Asthma concordance is more common among monozygotic than dizygotic twins, indicating a strong genetic predisposition (10, 17). However, some monozygotic twins are discordant for allergic diseases, suggesting that environmental factors affect the development of allergic diseases (9, 10, 17, 28). Furthermore, sudden

Table 2. Mean Co-HSA RAST indices by lifestyle category in nonexposed male subjects while controlling for age. Note that similar results were obtained in the exposed male subjects after controlling for exposure doses

Health practice	Good lifestyle		Poor lifestyle	
	Category	Mean Co-HSA RAST index	Category	Mean Co-HSA RAST index
1. Regularity of daily life	regular	1.27±0.15	irregular	1.28±0.15
2. Enjoying hobbies	yes	1.26±0.15	no	1.28±0.15
3. Feeling busy	no	1.27±0.15	yes	1.29±0.15
4. Physical exercise	≥2/wk	1.28±0.14	≤1/wk	1.26±0.15
5. Alcohol consumption	not every day	1.28±0.16	every day	1.27±0.15
6. Smoking habits	never	1.26±0.16	present/former	1.29±0.16
7. Sleeping pattern	7–8 h	1.27±0.15	≤6 h, ≥9 h	1.28±0.15
8. Regularity of eating	regular	1.27±0.14	irregular	1.28±0.16
9. Nutritional balance	good	1.28±0.16	poor	1.27±0.16
10. Eating breakfast	every morning	1.28±0.16	not every morning	1.28±0.15
11. Tea or coffee	≤4 cups/day	1.27±0.16	≥5 cups/day	1.30±0.15
12. Working pattern	<9 h	1.28±0.14	≥9 h	1.24±0.16
13. Subjective mental stress	mild	1.28±0.15	strong/weak	1.26±0.16
14. Conditional change	better/no change	1.28±0.15	worse	1.27±0.15
15. Life satisfaction	great	1.31±0.15	little	1.26±0.14
16. Snacking	no	1.28±0.15	every day/often	1.27±0.14
17. Salt consumption	good control	1.28±0.16	poor control	1.27±0.14

development, exacerbation, disappearance, or remission of allergic reactions among patients are often found in outpatient clinics without any change in therapeutic and environmental factors. These findings suggest that lifestyle factors, including mental health status, can modulate allergic reactions which are dependent on IgE antibodies. Our previous investigation was focused on the strong association between total IgE antibodies and “comprehensive lifestyles” that was established by our newly developed, self-administered questionnaire (25). Our present interest was therefore focused on the dynamics among lifestyles, and total and specific IgE antibodies.

Our first approach was an assessment of dose-response relationship between the antigen and specific IgE antibodies. For this reason, we could not study subjects by tests using common airborne antigens such as those of mites or pollen because of our inability to determine to what extent and for how long each subject might previously have been exposed to them. We therefore chose a particular occupational population (hard metal workers) for study. Percent binding of specific IgE antibodies to Co-HSA was in the range 0.78–2.08. This value was certainly higher than that of specific IgE against TCPA-HSA with the range –0.38 to 31.16% (30). However, our knowledge of the distribution of specific IgE antibodies against metal hapten conjugates remains too rudimentary to allow further comparison of the specific RAST sensitivities. As shown in Fig. 1B, there was a significant ($P<0.05$) association between hard metal (cobalt) exposure and elevated Co-HSA RAST indices in male subjects:

(1.16 ± 0.13 in nonexposed subjects; 1.37 ± 0.13 in exposed), with a strong ($P<0.001$) correlation with cobalt intensity and doses. A similar phenomenon has been documented among workers exposed to TCPA, in whom skin test sensitivity and specific IgE responses were associated (30). Further study is needed to examine the relationship between skin test reactivity and the Co-HSA RAST index in an occupational population exposed to hard metal.

Our second approach was to examine the relationship between lifestyle and specific IgE antibodies. Of 17 health practices examined, some are well known to increase (smoking) (3, 4, 5, 7, 11–16) or decrease (severe malnutrition) (21, 22) specific IgE antibodies. Stress has also been known to modulate specific IgE levels in animal experiments (20). However, no significant difference was found between *good* and *poor* categories in any of the 17 items while controlling for sex, age, exposure status, and total IgE levels (Table 2): an age-related increase in specific IgE was evident, but it was nonsignificant ($P=0.09$) in its linearity, and there was no difference by sex. Discrepancies in the influence of smoking and nutritional factors on specific IgE may be due to differences in lifestyles and/or environmental factors among the populations studied.

Each of these physical and mental practices also made no independent contribution to increasing or decreasing total IgE levels (25). However, total IgE level was significantly dependent upon “comprehensive lifestyles”, as shown by a new index, HPIA, in which eight practices were extracted by MANOVA analysis (27) while sex, age, and exposure doses were controlled for (25). This finding offers a further hypo-

thesis that HPIA might play a significant role in modulating Co-HSA RAST indices as found in total IgE. There was a certain trend for specific IgE to decrease with HPIA score. However, no cumulative effect of lifestyles was found on specific IgE when total IgE was in the normal zone (5–400 IU/ml). However, a dramatic synergism of *unhealthy* lifestyle was associated with specific IgE elevation to high-risk status (Co-HSA RAST > mean + 2 SD; RR > 2.0; $P < 0.05$ in Table 1) when total IgE level was in high-risk status (>400 IU/ml) for allergy. According to our results, to prevent type I allergy, patients with high levels of total IgE should avoid the *unhealthy* lifestyles found in this study.

Further interest should now be focused on the effects of lifestyles on specific and total IgE levels. Specific IgE has been regarded as part of total IgE antibodies. However, environmental as well as lifestyle factors play an independent role in modulating these two antibodies. Our results might offer a new model of specific and total IgE antibodies in which these two antibodies independently increase or decrease. This is further supported by the molecular genetic demonstration that the former is regulated by HLA-D (R or Q) loci, while the latter is thought to be associated with the autosomal dominant gene (9).

We can apply these principles to a general population study with relation to dose-response relationships for common airborne allergens. These include those of pollen, mites, and fungi. This offers a further strategy for the prevention of allergic disorders.

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