The concentrations of air pollutants, represented by suspended particulate matter (SPM) and nitrogen dioxide (NO₂), have increased due to the increase in motor vehicle traffic in urban areas in Japan. The effects of such air pollution on human health become of major concern. For children, most epidemiologic studies have focused on the effect of air pollution on respiratory symptoms or disease. There has long been a need for sensitive biomarkers to objectively evaluate the chronic effects of air pollution on human health as early as possible, but none has yet been identified. Previously, we reported an association between serum concentrations of acute phase proteins or hyaluronate in children and concentrations of air pollutants, but assays for these serum factors have not been validated as biomarkers for the effects of air pollution.

C-reactive protein (CRP) in serum has been widely used as a marker for infectious disease. A population-based study in Finland reported the association of serum CRP concentration with bronchial asthma. Because high-sensitivity tests of CRP are now available, it is possible to detect slight inflammatory conditions or local tissue damage that would have been undetectable by previous methods. Serum CRP concentration has been reported to be useful for prediction of cardiovascular disease, because such concentrations have been associated with atherosclerosis. Furthermore, acute effects of particulate air pollution on serum
CRP concentration have been previously documented in adults.14-18 Although the acute effect of air pollution on serum CRP has also been observed in healthy young people,19 there are no reported studies of the association between serum CRP concentration and chronic exposure to air pollution. Therefore, the author conducted a cross-sectional study in 3 communities with different concentrations of air pollutants, and measured serum CRP concentration in school children. The levels of serum CRP were examined for association with sex, age, respiratory symptoms, and various environmental factors.

Study Population
The study population consisted of the entire children (2,540 pupils, grades 1-6, aged 6-12 years) attending 6 elementary schools from 3 different communities in Chiba Prefecture, Japan (Figure). Of these schools, three were in an urban district next to the Tokyo metropolitan area (Ichikawa), and located near major roads. The distance between a school and a road ranged from 50 to 700 m. Of the other schools, one was located in the interior of the Boso Peninsula (Obitsu) and two were adjacent to the coast of Tokyo Bay (Kimitsu). There were no major roads near these three schools.

Air Pollution Measurements
Air pollutants are monitored continuously by the local authorities of the Chiba Prefectural Government. In Japan, particulate air pollution is assessed based on the concentration of SPM, which is the fraction of particles with a diameter less than 10 µm. The usual concentration of SPM corresponds approximately to that of particles passing an inlet with 50% cut-off efficacy using an aerosol dynamic diameter of 7 µm (PM7).20 The average concentrations of SPM, NO2, and sulfur dioxide (SO2) for the 3-year period from 1998 through 2000, measured at monitoring stations proximal to the study schools, are shown in Table 1. The distance between a school and a monitoring station ranged from 0 to 1.4 km. All concentrations measured were lowest in Obitsu. The concentrations in Kimitsu, which is located in an industrial area, were moderately high. All 3 stations in Ichikawa, which has heavy motor vehicle traffic, had the highest concentrations of air pollutants. The concentrations of air pollutants did not change substantially during the study period. The correlation between SPM and NO2 was high (correlation coefficient = 0.86). The concentration of SO2 also showed very strong correlation with SPM and NO2 (correlation coefficients = 0.99 and 0.92, respectively).

Table 1. Average concentrations of atmospheric air pollutants in the study communities.

| Community       | SPM (µg/m³) | NO2 (ppb) | SO2 (ppb) |
|-----------------|-------------|-----------|-----------|
| Ichikawa (A)    | 41.7 (3.2)  | 25.3 (2.5)| 6.3 (0.6) |
| Ichikawa (B)    | 42.7 (2.9)  | 23.7 (1.5)| 6.3 (0.6) |
| Ichikawa (C)    | 40.3 (6.5)  | 29.0 (2.0)| 6.3 (1.5) |
| Kimitsu         | 28.0 (1.0)  | 19.0 (1.0)| 4.7 (1.2) |
| Obitsu          | 26.7 (2.5)  | 11.7 (2.1)| 4.3 (0.6) |

*: Data are shown as the mean values (SD) of the annual average concentrations of air pollutants for the 3 year period 1998-2000, measured at ambient air monitoring stations located near the study schools.

SPM: Suspended particulate matter
NO2: Nitrogen dioxide
SO2: Sulfur dioxide
ppb: parts per billion
SD: Standard deviation
Because the serum CRP concentration was undetectable among more than half the children, the concentrations were then dichotomized at the 90th percentile (1.4 mg/L), and the prevalence of a serum CRP concentration of 1.4 mg/L or above was compared in relation to various factors. To evaluate the effects of each factor, multiple logistic regression analyses were performed using the high serum CRP concentrations as a binary outcome. The 3-year average concentrations of air pollutants in the communities where the children lived were included in the models as continuous variables. Statistical analyses were performed using SPSS® software (SPSS Inc., Chicago, IL, USA).

Questionnaires were collected from 2,501 children (98.5%), blood samples were collected from 2,097 children (82.6%), and usable data for both were obtained from 2,094 children (82.4%). The characteristics of the study children are shown according to study communities in Table 2. There were no differences in sex, age, asthma or wheezing, or serum IgE concentrations in the children from the 3 communities. The proportion of bottle-fed children was higher in Obitsu than in other communities, while that of breast-fed children was higher in Ichikawa. However, the propor-

| Table 2. Demographics and health characteristics (%) of the study subjects, by community. |
|---------------------------------|--------|--------|--------|--------|
| Sex                             | Ichikawa | Kimitsu | Obitsu | p value |
| Male                            | 50.0    | 52.5    | 51.6   | 0.577   |
| Female                          | 50.0    | 47.5    | 48.4   |         |
| Age (year)                      |         |        |        |         |
| 6-7                             | 22.2    | 26.1    | 22.1   | 0.227   |
| 8-10                            | 49.1    | 47.7    | 46.9   |         |
| 11-12                           | 28.7    | 26.1    | 31.0   |         |
| Mean age (years) (SD)           | 9.19    | 9.02    | 9.24   | 0.068   |
| Feeding method in infancy       |         |        |        |         |
| Bottle                          | 18.2    | 26.5    | 36.6   | <0.001  |
| Breast                          | 34.9    | 25.7    | 18.3   |         |
| Mixed                           | 46.9    | 47.7    | 45.1   |         |
| Familial smoking habits         |         |        |        |         |
| Mother smokes                   | 18.3    | 21.7    | 11.8   | <0.001  |
| Others smoke                    | 40.1    | 44.4    | 56.9   |         |
| No one smokes                   | 41.5    | 33.9    | 31.3   |         |
| Respiratory symptoms            |         |        |        |         |
| Wheezing                        | 6.0     | 7.1     | 4.4    | 0.292   |
| Asthma                          | 8.4     | 8.0     | 6.2    |         |
| No symptoms                     | 85.5    | 84.9    | 89.4   |         |
| Serum IgE concentration         |         |        |        |         |
| 0-249 IU/mL                     | 69.8    | 69.4    | 65.8   | 0.37    |
| ≥ 250 IU/mL                     | 30.2    | 30.6    | 34.2   |         |

SD: Standard deviation
The proportion of smoking mothers in Obitsu was low. In contrast, the proportion of family members who were smokers, other than mothers, was significantly higher in Obitsu than in other communities.

Table 3 shows the results of univariate analysis of serum CRP concentration and the prevalence of a serum CRP concentration of the 90th percentile (1.4 mg/L) or above, according to sex, age, feeding method in infancy, familial smoking habits, respiratory symptoms, serum IgE concentrations, and study communities. The serum CRP concentration was highest in the youngest children (6-7 years), and decreased with age. The prevalence of a serum CRP concentration of the 90th percentile or above was highest in children aged 6-7 years. Children who were bottle-fed in infancy had significantly higher serum CRP concentrations than children who were either breast- or mixed-fed. The serum CRP concentration in children whose mothers were smokers was significantly higher than in children without smokers in the family. The smoking habits of family members other than mothers were not significantly related to serum CRP concentration. The serum CRP concentration in children with wheeze was higher than in children without wheeze. The prevalence of a serum CRP concentration of the 90th percentile or above was also higher in children with wheeze. Children with asthma had higher serum CRP concentrations than those without, but the difference was not statistically significant. Analysis of serum CRP concentration

| Table 3. Univariate analysis of serum C-reactive protein (CRP) concentration (mg/L) and prevalence (%) of CRP ≥ the 90th percentile (1.4 mg/L) in children relative to various factors. |
|---|---|---|---|
| **Sex** | n | **Geometric mean (mg/L)** | **CRP ≥ 1.4 mg/L** |
| | | (95% CI) | p value | % | p value |
| Male | 1072 | 0.36 (0.34-0.38) | 0.349 | 10.5 | 0.619 |
| Female | 1022 | 0.35 (0.33-0.37) | 9.9 |
| **Age (years)** | | | | | |
| 6-7 | 494 | 0.46 (0.42-0.51) | <0.001 | 16.4 | <0.001 |
| 8-10 | 1011 | 0.34 * (0.32-0.36) | 9.7 |
| 11-12 | 589 | 0.29 ** (0.27-0.31) | 5.9 |
| **Feeding method in infancy** | | | | | |
| Bottle | 506 | 0.4 (0.36-0.44) | 0.002 | 13.8 | 0.009 |
| Breast | 606 | 0.34 ^ (0.32-0.37) | 8.9 |
| Mixed | 982 | 0.34 ^ (0.32-0.35) | 9.2 |
| **Familial smoking habits** | | | | | |
| Mother smokes | 387 | 0.41 (0.37-0.46) | <0.001 | 14.2 | 0.014 |
| Others smoke | 929 | 0.35 ^ (0.33-0.37) | 9.7 |
| No one smokes | 778 | 0.33 ^ (0.31-0.35) | 8.9 |
| **Respiratory symptoms** | | | | | |
| Wheezing | 129 | 0.47 (0.38-0.57) | <0.001 | 17.8 | 0.002 |
| Asthma | 166 | 0.41 (0.35-0.47) | 13.9 |
| No symptoms | 1799 | 0.34 ^ (0.33-0.36) | 9.3 |
| **Serum IgE concentration** | | | | | |
| 0-249 IU/mL | 1445 | 0.35 (0.33-0.37) | 0.475 | 10.1 | 0.794 |
| ≥ 250 IU/mL | 649 | 0.36 (0.33-0.39) | 10.5 |
| **Study community** | | | | | |
| Ichikawa | 1009 | 0.36 (0.34-0.38) | 0.483 | 11.3 | 0.259 |
| Kimitsu | 746 | 0.35 (0.33-0.37) | 9.5 |
| Obitsu | 339 | 0.34 (0.31-0.37) | 8.6 |

The significance of the differences in serum CRP concentration among the groups was evaluated by Tukey’s method.

*: p<0.01 compared with children 6-7 years old.
**: p<0.01 compared with children 8-10 years old.
***: p<0.05, ****: p<0.01 compared with children who were bottle-fed in infancy.
**: p<0.01 compared with children whose mothers smoke.
***: p<0.01 compared with children with wheeze.

CI: confidence interval
according to study among community revealed that the concentrations were highest in Ichikawa among the three communities, followed by Kimitsu, and then Obitsu, however these differences were not statistically significant. The differences in serum CRP concentration according to sex and serum IgE concentrations were not statistically significant.

The effects of various factors on serum CRP concentration of the 90th percentile or above were analyzed using logistic regression analysis (Table 4). The adjusted odds ratio (OR) of high serum CRP concentration for age was significantly below one. High serum CRP concentration was also significantly associated with bottle-feeding in infancy, maternal smoking habit and wheezing. The association of high serum CRP concentration with SPM concentration in the communities where the children lived was significant (OR = 1.49 for the range of observed concentrations, 95% CI: 1.07-2.06). High serum CRP concentration was also associated with SO2 concentration (OR =1.45 for the range of observed concentrations, 95% CI: 0.87-2.28). In a two-pollutant model including SPM and NO2 concentrations, high serum CRP concentration was also significantly associated with SO2 concentration (OR =1.45 for the range of observed concentrations, 95% CI: 0.87-2.28). In a two-pollutant model including NO2 concentration and SO2 concentration were not statistically significant (OR = 1.49 for the range of observed concentrations, 95% CI: 1.07-2.06). High serum CRP concentration was also significantly associated with SPM concentration in the communities where the children lived was significant (OR = 1.49 for the range of observed concentrations, 95% CI: 1.07-2.06). High serum CRP concentration was also significantly associated with NO2 concentration (OR =0.62 for the range of observed concentrations, 95% CI: 0.26-1.48). Because SO2 concentration strongly correlated with SPM and NO2, two-pollutant models including SO2 concentration were not analyzed.

In models without respiratory symptoms and /or serum IgE concentration, the results were essentially the same (data not shown).

**CRP is one of the major acute-phase proteins in humans. It is produced mainly by the liver, and its production is regulated by cytokines, including interleukin-6. The production of CRP is enhanced when the complement system is activated by inflammatory reactions that accompany bacterial infections or tissue injury in vivo. Therefore, serum CRP concentration has frequently been used as a marker for inflammation.**

The author and coworkers previously reported that the serum concentrations of the acute-phase proteins C3c and C4 in children reflect their exposure level to air pollutants. In addition, the serum C3c concentration in boys is significantly increased by exposure to environmental tobacco smoke. In these previous studies, children with symptoms of a cold or fever were excluded to eliminate the effects of acute inflammation. Therefore, the serum CRP concentration in most children was below the detection level of 3.0 mg/L. A newly available assay for measuring

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**Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for various factors on C-reactive protein (CRP) ≥ the 90th percentile (1.4 mg/L).**

| Factor                        | A single-pollutant model including SPM concentration (OR (95% CI)) | p value | A single-pollutant model including NO2 concentration (OR (95% CI)) | p value | A single-pollutant model including SO2 concentration (OR (95% CI)) | p value | A two-pollutant model including SPM and NO2 concentrations (OR (95% CI)) | p value |
|-------------------------------|-----------------------------------------------------------------|---------|-----------------------------------------------------------------|---------|-----------------------------------------------------------------|---------|-----------------------------------------------------------------|---------|
| Age (1 year increase)         | 0.83 (0.76-0.90)                                                 | <0.001  | 0.83 (0.77-0.90)                                                 | <0.001  | 0.83 (0.76-0.90)                                                 | <0.001  | 0.83 (0.76-0.90)                                                 | <0.001  |
| Sex (females vs. males)       | 0.92 (0.69-1.23)                                                 | 0.581   | 0.93 (0.70-1.24)                                                 | 0.621   | 0.92 (0.69-1.24)                                                 | 0.594   | 0.92 (0.69-1.23)                                                 | 0.562   |
| Bottle-fed                    | 1.67 (1.22-2.28)                                                 | 0.001   | 1.63 (1.19-2.23)                                                 | 0.002   | 1.66 (1.22-2.27)                                                 | 0.001   | 1.65 (1.21-2.26)                                                 | 0.002   |
| Maternal smoking              | 1.48 (1.06-2.07)                                                 | 0.023   | 1.47 (1.05-2.06)                                                 | 0.024   | 1.48 (1.06-2.07)                                                 | 0.023   | 1.49 (1.06-2.08)                                                 | 0.021   |
| Serum IgE concentration (≥ 250 IU/mL vs. 0-249 IU/mL) | 1.09 (0.77-1.53)                                                 | 0.624   | 1.09 (0.78-1.53)                                                 | 0.619   | 1.09 (0.77-1.53)                                                 | 0.621   | 1.09 (0.77-1.53)                                                 | 0.628   |
| Respiratory symptoms          |                                                               |         |                                                               |         |                                                               |         |                                                               |         |
| Wheezing                      | 1.85 (1.11-3.08)                                                 | 0.018   | 1.84 (1.11-3.06)                                                 | 0.018   | 1.85 (1.11-3.07)                                                 | 0.018   | 1.86 (1.12-3.10)                                                 | 0.017   |
| Asthma                        | 1.58 (0.95-2.63)                                                 | 0.078   | 1.59 (0.95-2.64)                                                 | 0.076   | 1.58 (0.95-2.63)                                                 | 0.077   | 1.58 (0.95-2.63)                                                 | 0.078   |
| No symptoms                   | 1.00 (referene)                                                 |         | 1.00 (referene)                                                 |         | 1.00 (referene)                                                 |         | 1.00 (referene)                                                 |         |
| SPM (range: 26.7-42.7 µg/m³)   | 1.49 (1.07-2.06)                                                 | 0.017   | -                                                               | -       | -                                                               | -       | 1.94 (1.08-3.50)                                                 | 0.027   |
| NO2 (range: 11.7-29.0 ppb)     | 1.41 (0.87-2.28)                                                 | 0.164   | -                                                               | -       | -                                                               | -       | 0.62 (0.26-1.48)                                                 | 0.287   |
| SO2 (range: 4.3-6.3 ppb)       | -                                                               | -       | 1.45 (1.04-2.03)                                                 | 0.031   | -                                                               | -       | -                                                               |         |

Two-pollutant models including SO2 concentration were not analyzed, because the SO2 concentration very strongly correlated with SPM and NO2 (correlation coefficients = 0.99 and 0.92, respectively).

*: ORs were adjusted for all variables using each logistic regression model

SPM: Suspended particulate matter
NO2: Nitrogen dioxide
SO2: Sulfur dioxide
ppb: parts per billion
CRP concentration has a detection level of 0.2 mg/dL, and has been found to be useful for early detection of infectious disease in newborns and immature infants. This serum CRP assay is considered to be particularly useful for evaluation of mild chronic inflammation in apparently healthy individuals.

In the present study, the author conducted a cross-sectional study in 3 communities with different concentrations of air pollutants, and examined the serum CRP concentration in children. Serum CRP concentration differed significantly according to age, feeding method in infancy, maternal smoking habit, and wheezing. There were differences in feeding method in infancy and maternal smoking habit among the study communities. Multiple logistic regression analyses adjusted for these potential confounding factors showed that serum CRP concentrations of the 90th percentile or above were significantly associated with SPM concentration in each community. These findings suggest that air pollution affects serum CRP concentration in children, and are consistent with the results of previous reports showing an association between air pollution and concentrations of serum acute-phase proteins. Children with signs of acute inflammation were excluded from the present study, eliminating the possibility that reported differences were due to an epidemic of inflammatory diseases. In multivariate models without respiratory symptoms and/or serum IgE concentration, the associations between air pollutants and serum CRP concentration were essentially the same.

Serum CRP concentration is associated with factors such as age, obesity, and smoking habit. In chronic inflammation, a slight elevation in serum CRP concentration can persist. Therefore, serum CRP has been considered a useful marker for prediction of cardiac infarction or for evaluation of inflammation of blood vessels due to atherosclerosis in adults. A study in elderly people showed that serum CRP concentration increases with age, because older people are subject to the effects of low grade inflammation due to chronic disease. Adults with serum CRP concentrations of 3 mg/L or above are considered at high risk for cardiovascular diseases. The serum CRP concentration is reportedly lower in children than adults. In the present study, the concentrations were then dichotomized at the 90th percentile (1.4 mg/L). Serum CRP concentration was highest in the youngest children, and decreased with age among school children under 12 years old. Because younger children easily contract respiratory infections, low grade inflammation due to subclinical respiratory conditions may influence serum CRP concentration in young children.

The serum CRP concentration in children with wheeze was significantly higher than in children without wheeze. A population-based study in Finland reported that the prevalence of asthma increased gradually with increasing serum CRP concentration. Inflammation in the respiratory tract is thought to play an important role in the pathological conditions of wheezing and asthma. Wheezing is often caused by a viral infection. In the present study, the serum CRP concentration was slightly higher in children with asthma than those without, but the difference was not significant, possibly because most asthmatic children were asymptomatic when examined. An allergic predisposition, accompanied by increases in serum IgE concentration, is thought to be important for the development of the pathological states of childhood asthma. However, the author believes that no direct relationship exists between allergies and serum CRP concentration, because no association was found between serum IgE and CRP concentration.

The serum CRP concentration in children with mothers who smoked was significantly higher than those in children with non-smoking mothers. The serum CRP concentration in smokers is higher than in non-smokers. The author previously reported that concentrations of acute-phase proteins in children were elevated upon exposure to environmental tobacco smoke, and suggested the possibility that passive smoking may lead to slight inflammation in children. In the present study, the effects of smoking by family members other than mothers, i.e., mainly fathers, were not detected. This may reflect the lack of opportunity for fathers to smoke when with their children.

The complement activities of children who were bottle-fed in infancy have been reported to be high. Children who were both bottle- and breast-fed have been reported to have higher CRP concentrations than those who were only breast-fed. In the present study, children who were only bottle-fed had higher serum CRP concentrations than those who were only breast-fed or those who received mixed-feeding. The reason for this is not clear, but might be related to the protective effects of breast-feeding against infection during infancy.

No significant difference in serum CRP concentration according to sex was observed. A study based on 3605 subjects found no differences in serum CRP concentration by sex between 5-39 years of age. Cook et al determined a relationship between serum CRP concentration in children and adiposity and suggested an association between CRP and cardiovascular disease. The involvement of serum CRP concentration with various factors such as sex, adiposity, body constitution, and symptoms other than respiratory symptoms should be further evaluated.

Air pollution due to automobile exhaust is a serious problem in the urban areas of Japan. The effect of fine particles in diesel exhaust on human health has become a matter of concern. Recently, air quality standards for atmospheric concentration of particulate matter less than 2.5 µm in diameter (PM2.5) have been established in the United States and European countries. Because atmospheric concentrations of PM2.5 have been rarely measured in Japan, the effects of SPM, NO2, and SO2 were examined in the present study. When various confounding factors were adjusted for, increased serum CRP concentrations of the 90th percentile or above were significantly associated with SPM and SO2 concentration. The adjusted OR of high serum CRP concentrations for the range of observed NO2 concentrations was similar to that for SPM and SO2, but this was not significant. In a two-pollutant model including both SPM and NO2 concentrations, high serum CRP concentration was associated only with SPM.
These results suggest that SPM in the atmosphere may induce an inflammatory response in children more readily than NO₂. However, the concentrations of SPM and NO₂ are correlated, and the concentration of SO₂ showed stronger correlation with these air pollutants. Therefore, it is difficult to elaborate on which pollutant has a stronger effect on serum CRP concentration. In addition, the effects of specific characteristics of the communities where the children lived cannot be completely eliminated.

A slight elevation in serum CRP concentration is thought to reflect chronic inflammation *in vivo*. Acute effects of particulate air pollution on serum CRP concentration have been reported in middle-aged or elderly subjects, and in individuals with diabetes, obesity, hypertension, and coronary heart disease. Recently, an acute effect of particulate air pollution on serum CRP was also observed in healthy young people. A weak positive association between CRP and 60-day mean exposure to PM₂.₅ has been also reported. Because the concentrations of air pollutants did not change greatly during the study period, the chronic effect of air pollution on serum CRP concentration was examined using 3-year average concentrations of air pollutants. Induction of proinflammatory cytokines and CRP has also been reported in macrophage cell lines exposed to ambient air particulates. Particulate air pollution may cause slight chronic inflammation in the respiratory tract in children, and may induce an inflammatory response in humans more readily than NO₂. The pathophysiological significance of changes in serum CRP concentration is unknown, but is a topic worthy of additional study.

In conclusion, high serum CRP concentrations of the 90th percentile or above are associated with atmospheric concentrations of SPM. These findings suggest that air pollutants such as SPM may cause a slight inflammation *in vivo*. Slight elevations in serum CRP concentration, such as those observed in the present study, are thought to be a risk factor for cardiovascular disease and have been associated with particulate air pollution.

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