Temperature and Air Pollution as Risk Factors for Heat Stroke in Tokyo, July and August 1980–1995

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Heat stroke is associated with prolonged exposures to high air temperatures that usually occur in the summer months of July and August in Tokyo, Japan. Also during July and August, residents of Tokyo are often exposed simultaneously to high concentrations of air pollutants. To assess the impacts of these combined exposures, daily numbers of heat stroke emergency transport cases/million residents for Tokyo were stratified by gender and three groups: 0–14, 15–64, and > 65 years of age, for the months of July and August in 1980–1995. A regression model was constructed using daily maximum temperature (T\text{max}) and daily average concentrations of NO\textsubscript{x} and O\textsubscript{3} as model covariates. Classification indices were added to make it possible to compare the expected number of heat stroke cases by age and gender. Lag times of 1–4 days in T\text{max} and air quality covariates and terms to account for interactions between pairs of model covariates were also included as additional risk factors. Generalized linear models (GLMs), assuming a Poisson error structure for heat stroke emergency transport cases, were used to determine which covariates were significant risk factors for heat stroke for the three age groups of males and females. Same-day T\text{max} and concentrations of NO\textsubscript{x} were the most significant risk factors for heat stroke in all age groups of males and females. The number of heat stroke emergency transport cases/million residents was greater in males than in females in the same age groups. The smallest number of heat stroke emergency transport cases/million residents occurred for females 0–14 years of age and the greatest number of heat stroke emergency transport cases/million residents occurred for males > 65 years of age. Key words: air pollutants, generalized linear regression models, heat stroke, maximum daily temperatures. *Environ Health Perspect* 107:911–916 (1999). [Online 15 October 1999]

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The Intergovernmental Panel on Climate Change has projected that atmospheric concentrations of CO\textsubscript{2} could double in the next 50–100 years (1). Because of the greenhouse effect, a doubling of atmospheric concentrations of CO\textsubscript{2} could result in an increase in average global surface air temperatures of 1–3°C. In addition, because approximately 65% of atmospheric concentrations of CO\textsubscript{2} are from the combustion of fossil fuels, increasing concentrations of CO\textsubscript{2} could also be accompanied by increasing concentrations of air pollutants, particularly in large urban areas. An increase in surface air temperatures could be accompanied by a greater frequency and duration of heat waves. Because heat waves often occur in large metropolitan areas during warm summer months, these areas could experience an increase in the incidence of heat-related morbidity and mortality (2).

In Tokyo, Japan, heat waves occur most often during the warm summer months of July and August. Heat waves are characterized as periods of prolonged high daily average temperatures, high maximum and minimum temperatures, high relative humidities, and in many cases because of temperature inversions and/or stagnant air masses, high air pollutant concentrations. During a heat wave, hot days are often followed by hot nights because of the heat island effect. These weather and air quality conditions can produce a high degree of heat and air pollution stress, especially for people with cardiovascular and respiratory disorders. During heat waves, combined exposures to some or all of these factors often occur either on the same day or within a short time of each other. Because the frequency and duration of heat waves may increase as a result of increasing surface air temperatures, it is important to determine the extent to which some or all of these climate and air pollutant variables contribute to heat-related morbidity, particularly heat stroke. In addition, the impacts on different age groups of males and females as a result of these combined exposures must be determined.

Data and Model Development

Data on emergency transport cases for heat stroke to four large medical centers within the city limits of Tokyo were obtained from medical records compiled by the Tokyo Emergency Office (Tokyo, Japan). For the summer months of July and August in 1980–1995, heat stroke data were stratified by age and gender. The *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva) code for heat stroke is 992. Data were obtained for three male and female age groups: 0–14, 15–64, and > 65 years of age. A diagnosis of heat stroke could include heat cramps, heat exhaustion, and severe heat stroke, which is characterized by a core body temperature > 40.6°C and multiple organ dysfunction. The procedures for diagnosing heat stroke did not change during the 1980–1995 period. When the patient entered the emergency room, the attending physician made the diagnosis and admitted all people diagnosed with heat stroke to the hospital.

Daily numbers of heat stroke emergency transport cases/million residents in each age group of males and females for the months of July and August were determined from population data provided by the Japan Ministry of Health and Welfare in Tokyo. From 1980 to 1995, the total population within the city of Tokyo has remained nearly constant at approximately 11.8 million inhabitants. The population is approximately 50% male and 50% female. However, as shown in Table 1, the percentage of residents in the group > 65 years of age has increased and the percentage of residents in the group 0–14 years of age has decreased. Data were not available to subdivide the 15–64-year age group further, but the percentage of residents in this age group remained relatively constant from 1980 to 1995. Linear interpolation was used to estimate the number of people in each age group for those years in which population data were not available so that daily age-specific numbers of heat stroke emergency transport cases/million residents could be calculated for each age group of males and females from 1980 to 1995.

From 1980 to 1995, 85% of the heat stroke emergency transport cases (2,060 cases of a total of 2,422) occurred in either July or August. The daily average July and August...
number of heat stroke emergency transport cases/million residents from 1980 to 1995 are shown for males and females in each age group in Figure 1. This graph indicates that the daily average number of heat stroke emergency transport cases/million residents was greater for males than for females for the same age groups, and that the daily average number of heat stroke emergency transports/million residents were greatest for males and females > 65 years of age. In many instances, the daily average number of heat stroke emergency transport cases/million residents in males 15–64 years of age were almost as high as for males and females > 65 years of age. These results suggested that regression models for heat stroke should be structured to compare expected daily numbers of heat stroke cases by gender and age.

An additional consideration in the development of regression models for heat stroke was the daily average number of heat stroke emergency transport cases/million residents for males 15–64 and > 65 years of age and females > 65 years of age that were observed in 1981, 1984, 1987, 1990, and 1994–1995. These observations suggested that models for heat stroke needed to account for annual changes in the number of heat stroke cases for each age group of males and females.

Because exposures to high daily maximum temperatures ($T_{\text{max}}$) have been strongly associated with heat stroke ($T_{\text{max}}$), it was important to understand how daily averages in $T_{\text{max}}$ were changing from 1980 to 1995 and how they were related to the average daily number of heat stroke emergency transport cases/million. Figure 2 is a plot of daily average $T_{\text{max}}$ temperatures for July and August 1980–1995 and the average daily number of heat stroke emergency transport cases/million for males and females > 65 years of age. The correspondence between the peaks in the number of heat stroke cases and the peaks in $T_{\text{max}}$ suggest that a regression model which used $T_{\text{max}}$ as a covariate would best simulate conditions of maximal heat stress.

Figure 3 shows the frequency of occurrence of heat stroke in the three age groups of males and females for July and August 1980–1995. For most days, there were no emergency transport cases for heat stroke in all age groups of males and females. These results, along with calculated means and standard deviations for the densities of each age group of males and females, indicated that the daily number of heat stroke emergency transport cases for each age group of males and females were rare and were assumed to be Poisson distributed.

For a regression model for heat stroke, citywide daily concentrations of air pollutants and climate variables were obtained from the Japan Environment Agency (Tokyo, Japan). Daily 24-hr averages for each climate and air pollutant variable used in these analyses were calculated from pooled hourly measurements from four measurement locations within the city. $T_{\text{max}}$ (°C) data were also obtained from this same data set. From these records, daily averages were calculated for NO$_x$ concentrations (ppb), photochemical oxidant concentrations (ppb); concentrations of particles with mean diameters ≤10 μm (PM$_{10}$; μg/m$^3$); air temperatures ($T_{\text{w}}$; °C); and relative humidities (%). For Tokyo, approximately 80–85% of photochemical oxidant concentrations were composed of O$_3$. Therefore, O$_3$ (ppb) was used throughout this study as the surrogate for photochemical oxidant concentrations.

A regression model using the heat index as a model covariate was also considered. The heat index combines temperatures that are ≥21°C with relative humidities in a formula given by Stedman (4), and makes it possible to combine two important climate variables into one variable. However, the pathophysiology of heat stroke is difficult to interpret with the heat index because the temperature contribution to the heat index is difficult to isolate. As a result, a regression model for heat stroke that used the heat index as a model covariate was not considered further in this analysis.

Correlations of all pairs of covariates indicated that NO$_x$ and PM$_{10}$ were moderately collinear, r = 0.59. To determine which of these concentrations should be used in the analysis of heat stroke, linear regression analyses of heat stroke as functions of only NO$_2$, of only PM$_{10}$, and of the linear combination of $T_{\text{max}}$, NO$_2$, and PM$_{10}$ were carried out. Results of these model studies indicated that PM$_{10}$ concentrations were not significant contributing risk factors for heat stroke for both males and females in any age group whereas concentrations of NO$_2$ were. As a result, PM$_{10}$ concentrations were not considered further as a risk factor for heat stroke. Table 2 contains summary statistics for all model covariates.

**Analysis Methods**

Generalized linear models (GLMs) were used to determine which of the model covariates were significant risk factors for heat stroke (5). A GLM was used instead of an autoregressive-integrated-moving-average (ARIMA) time-series model because the number of daily heat stroke emergency transport cases was count data (6). To filter out any unmeasured long-term trends in the daily number of heat stroke cases that may have occurred...
from 1980 to 1995, 15 index variables for each year except the reference year (1980) were incorporated into the models to account for annual trends. Although it is possible that part of the long-term annual trend is due to temperature and air pollution fluctuations, it is often thought that confounding by other factors has a smaller influence when dealing with short-term air pollution and temperature effects than when dealing with longer term effects (7). Seasonal patterns were not explicitly adjusted for because only data for July and August from each year were used in this study. Adjustment terms, known as offsets in Poisson regression models, were included to account for population changes in Tokyo from 1980 to 1995.

Because it was possible that $T_{\text{max}}$ and concentrations of $\text{NO}_2$, $\text{O}_3$, and $\text{PM}_{10}$ on previous days could affect the number of heat stroke emergency transport cases on the current day, lag times of 1–4 days for each of these covariates were initially included in the models as additional risk factors. Model covariates were also centered using their means, as given in Table 2. The final model was determined using a backward selection process in which model covariates were examined for their statistical significance. Age, gender, and annual trend variables were always included in all models. Once the final model was determined, terms to account for interactions among all pairs of model covariates were also considered.

The daily number of heat stroke cases on any given day are likely to be correlated with the number of heat stroke cases on previous days. To account for serial correlations of heat stroke cases, model parameters in the GLMs were estimated using generalized estimating equations (GEEs) with the assumption of Poisson error (mean and variance are equal) and with a constant dispersion parameter (7,8). The correlation matrix for daily number of heat stroke cases within each year was assumed to be autoregressive. Responses from different years were assumed to be independent. Regression analyses were carried out with SAS software using the GENMOD procedure (9).

**Results and Discussion**

Based on $p$-value calculations for model parameters, same-day $T_{\text{max}}$ and $\text{NO}_2$ were the most significant risk factors for heat stroke in males and females in all three age groups. The parameter estimates for concentrations of $\text{O}_3$ had a $p$-value of 0.06 and were excluded from the final model. Lag effects in all model covariates were also determined not to be significant. The final model thus included $T_{\text{max}}$, $\text{NO}_2$, gender, age, and annual trend variables. All pairwise interactions among $T_{\text{max}}$, $\text{NO}_2$, age, and gender were not significant. However, age and gender were significant risk factors for heat stroke. Males had a higher risk for heat stroke than females in all age groups. The smallest risk for heat stroke occurred for females 0–14 years of age and the greatest risk for heat stroke occurred for males > 65 years of age. Parameter estimates and their $p$-values for this model are given in Table 3. The estimate of the overdispersion factor for this model was nearly equal to 1.0.

**Table 2. Summary statistics for model covariates.**

| Variable (units) | df | Min | Max | Mean ± SD |
|------------------|----|-----|-----|-----------|
| $T_{\text{max}}$ (°C) | 992 | 17.3 | 36.5 | 28.9 ± 3.8 |
| $\text{NO}_2$ (ppb) | 988 | 5.3 | 72.2 | 25.4 ± 11.4 |
| $\text{O}_3$ (ppb) | 990 | 0.05 | 59.4 | 13.9 ± 9.8 |
| $\text{PM}_{10}$ (µg/m$^3$) | 902 | 7.3 | 85.4 | 40.0 ± 27.1 |

Abbreviations: df, degrees of freedom; Max, maximum; Min, minimum; PM$_{10}$, particles ≤ 10 µm in aerodynamic diameter; SD, standard deviation; $T_{\text{max}}$, maximum daily temperature.
With this model, the expected daily number of heat stroke emergency transport cases/million for each age group of males and females is given as

\[ HS = \exp(\alpha + \beta_1 \times (T_{\text{max}}) + \beta_2 \times (\text{NO}_2)) \]

where HS is the expected daily number of heat stroke emergency transport cases/million residents for each age group of males and females; \( \alpha \) is the intercept; \( \beta_1 \) is the slope for \( T_{\text{max}} \) for all age groups of males and females; and \( \beta_2 \) is the slope for \( \text{NO}_2 \) concentrations for all age groups of males and females. The terms in Table 3, designated gender_m, age > 65 and age 15–64, are adjustments to the intercept (\( \alpha \)) and make it possible to compare the expected number of heat stroke emergency transport cases/million by age and gender.

Heat stroke has always been strongly associated with exposure to high temperatures and has been classified as either exertional or classic. Exertional heat stroke is more likely to be observed in healthy people who have been working or playing too hard during periods of high air temperature and high humidity and is usually observed in younger and middle-aged males and females. Classic heat stroke results from prolonged exposures to high air temperatures and humidity and occurs most often in elderly adults, the very young, and the chronically ill of all ages. Along with high core body temperatures, classic heat stroke patients often exhibit multiple organ dysfunction and many neurologic abnormalities. It was not possible to distinguish between these types of heat stroke from the data provided by the Tokyo Emergency Office.

During the Chicago, Illinois, heat wave of July 1995, the most common comorbid conditions that accompanied symptoms associated with classic heat stroke for 58 near-fatal heat stroke patients with a mean age of 67.5 (standard deviation = 17) were hypertension, alcohol abuse, coronary artery disease, and diabetes mellitus (10). In addition, 16 patients were taking diuretics and phenothiazines, medications that may predispose people to the development of heat stroke. Biological markers for heat stroke were described by Bouchama et al. (11), who showed that circulating concentrations of pyrogenic cytokines were elevated in patients with heat stroke. These cytokines included tumor necrosis factor-\( \alpha \), interleukin-6, interleukin-1 \( \beta \), and interferon-\( \gamma \). The authors suggested that the elevated levels of these pyrogenic cytokines were important in explaining the pathophysiology of multiple organ failure, shock, and hyperglycemia often observed in heat stroke patients.

An additional response to exposures to higher temperatures is the synthesis of heat shock proteins to protect vital cells, tissues, and organs from thermal damage (12,13). In the synthesis of heat shock proteins, studies in laboratory rats have shown that peroxidative damage from exposure to higher temperatures was greater in older male and female rats than in younger male and female rats (14). Peroxidative damage was mitigated by the production of the protective enzymes glutathione (GSH) peroxidase, GSH transferase, and catalase. As an indicator of the animal’s ability to adapt to higher temperatures, hepatic cytosolic GSH peroxidase activities were much higher in younger rats than in older rats. This study with laboratory animals suggested that the capacity to synthesize heat shock proteins diminished with age and compromised the animal’s ability to adapt to prolonged exposures to high temperatures.

Whereas exposure to high temperatures have been well established as a significant risk factor for heat stroke, exposures to elevated concentrations of \( \text{NO}_2 \) have usually been associated with respiratory disease disorders. The results of this study suggest that exposure to \( \text{NO}_2 \) are also significant risk factors for heat stroke in all age groups of males and females. Further, temperature and air quality conditions that produce high levels of heat and air quality stress may result in a greater risk for heat stroke in individuals with existing or preexisting respiratory and cardiovascular disorders.

There is considerable evidence that exposure to \( \text{NO}_2 \) reduces pulmonary vital capacity in humans. Investigators in the Harvard School of Public Health Six Cities Study extensively studied the effects of air pollutants on male and female children 7–11 years of age (15–23). In one study from this large prospective assessment program (23), a multiple logistic regression model was used to show that for a mean indoor \( \text{NO}_2 \) concentration of 14.4 ppb (range 10–19.9 ppb), the odds ratio for an increase in the prevalence of lower respiratory symptoms was 1.36 [95% confidence interval (CI), 0.89–2.08]; for a mean \( \text{NO}_2 \) concentration of 31 ppb (range 20–78.2 ppb), the odds ratio increased to 1.65 (CI, 1.03–2.63). During the summer months, indoor \( \text{NO}_2 \) concentration are close in magnitude to outdoor \( \text{NO}_2 \) concentration. Currently, the World Health Organization guideline exposure concentrations for \( \text{NO}_2 \) are an annual average of 53 ppb and a 1-hr maximum of 214 ppb (24).

Data for July and August 1980–1995 in Tokyo indicated that average daily \( \text{NO}_2 \) concentrations were > 50 ppb on 39 days (3.9%) and > 20 ppb on 638 days (64.3%). Concentrations of \( \text{NO}_2 \) only exceeded a 1-hr maximum of 100 ppb on 34 days (3.4%) and never exceeded 200 ppb during the months of July and August in 1980–1995. These studies on the effects of \( \text{NO}_2 \) exposures on pulmonary function in children indicate that respiratory dysfunction may also be important in the pathophysiology of heat stroke for the young and possibly for elderly adults.

It is not clear why there should be such a significant difference in the daily number of heat stroke emergency transport cases/million residents between male and female Tokyo residents > 65 years of age. The body’s response to heat stress is to return core body temperature to a normal range. This attempt to restore thermal equilibrium involves multiple organ systems and physiologic functions. The pathophysiologic consequences of heat stress for the elderly may be attributable to the collapse of multiple physiologic control systems. For elderly males, the strain on the cardiovascular system that is induced by the systemic response to heat stress may combine additively and/or synergistically with increased respiratory dysfunction from chronic obstructive pulmonary diseases, such as emphysema or asthma, in a manner that is greater than for elderly females. Reports from the July 1995 Chicago heat wave (10) and earlier studies on the heat wave in St. Louis and Kansas City, Missouri, in July 1980 (25,26) provided no information on differences in response for males and females or information on the presence or absence of chronic obstructive pulmonary diseases. The peaks in the daily numbers of heat stroke cases for males and females > 65 years of age in 1981, 1984, 1987, 1990, and 1994–1995 closely corresponded with peaks in \( T_{\text{max}} \), as shown in Figure 2.

### Table 3. Model risk factors for heat stroke, adjusted for annual trends.

| Model parameter       | Estimate (SE)ᵃ | Lower     | Upper     | Z-value | Pr > | 2ᵃ |
|-----------------------|----------------|-----------|-----------|---------|------|----|
| \( \alpha \)          | -3.88 (0.21)   | -4.29     | -3.48     | -18.67  | 0.0000 |    |
| \( T_{\text{max}} \)  | 0.48 (0.024)   | 0.433     | 0.527     | 20.13   | 0.0000 |    |
| \( \text{NO}_2 \)     | 0.016 (0.003)  | 0.01    | 0.022     | 5.61    | 0.0000 |    |
| Gender_m              | 1.054 (0.104)  | 0.85     | 1.26     | 10.1    | 0.0000 |    |
| Age > 65ᵇ             | 1.019 (0.17)   | 0.69     | 1.34     | 6.17    | 0.0000 |    |
| Age 15–64ᵇ            | 0.588 (0.134)  | 0.305    | 0.831     | 4.24    | 0.0000 |    |

**Abbreviations:** \( \alpha \), intercept; Age > 65, individuals > 65 years of age; Age 15–64, individuals 15–64 years of age; Gender_m, male; Pr > |2|, p-value for the parameter estimate; SE, standard error; \( T_{\text{max}} \), maximum daily temperature; Z, parameter estimate/SE.

ᵃEstimate based on the assumption that data are Poisson distributed. *Adjustments to the \( \alpha \)
to ask why these annual peaks in $T_{\text{max}}$ in Tokyo occur and if they are related to other climatic events that may be useful in predicting when these high temperatures would occur during summer months in Tokyo. As a possible explanation of the relationship of $T_{\text{max}}$ in Tokyo to large-scale climatic events, data from the Climate Analysis Section of the University Corporation for Atmospheric Research [Boulder, CO; (27)] indicate that sea-surface temperatures in a region of the equatorial Pacific Ocean designated Niño region 3.4, bounded by 120°W–170°W by 5°S–5°N, were abnormally high (+ 0.4°C above mean seasonally adjusted sea-surface temperatures) in 1983, 1988, and 1990–1995. Abnormally high sea-surface temperatures in this region of the Pacific Ocean usually cause ocean temperatures along the coastlines of Japan to be warmer than usual and may explain the higher air temperatures observed in Tokyo in those years. Figure 4 compares the daily number of heat stroke emergency transport cases/million for males and females > 65 years of age with sea-surface temperature anomalies for Niño region 3.4 for July and August 1980–1995. The horizontal dotted lines in Figure 4 indicate the normal range of variability in sea-surface temperatures for this region in the Pacific Ocean (± 0.4°C).

Conclusions

When the parameter estimates given in Table 3 are used in Equation 1, the expected daily number of heat stroke emergency transport cases/million residents can be estimated for each age group of males and females over a wide range of $T_{\text{max}}$ and NO$_2$ concentrations. In Figure 5, the expected daily number of heat stroke emergency transport cases/million for male and female residents > 65 years of age is plotted as a function of daily $T_{\text{max}}$ and NO$_2$ concentrations. The graphs illustrate that the expected daily number of heat stroke emergency transport cases/million residents increases as a result of increasing NO$_2$ concentrations and $T_{\text{max}}$ and that the expected

![Figure 4. Comparison of July and August 1980–1995 daily number of heat stroke emergency transport cases/million for males and females > 65 years of age in Tokyo with SSTAs for Niño region 3.4 in the Pacific Ocean. SSTAs, sea-surface temperature anomaly. SSTAs Niño region 3.4 is bounded by 120°W–170°W by 5°S–5°N. The two dotted horizontal lines for SSTAs of ± 0.4°C represent normal variability for sea-surface temperatures during July and August for Niño region 3.4.](image_url)

![Figure 5. Graphs of regression equations for the expected daily number of heat stroke emergency transport cases/million for (A) males > 65 years of age and (B) females > 65 years of age as a function of daily $T_{\text{max}}$ and NO$_2$ concentrations in Tokyo, July and August 1980–1995. $T_{\text{max}}$, maximum daily temperature.](image_url)
daily number of heat stroke emergency transport cases/million is greater for males > 65 years of age than for females in the same age group.

Why the group > 65 years of age is the most vulnerable and why there are significant differences in response between males and females are important areas for additional research. In addition to a better understanding of the physiology and biochemistry of heat stroke as a result of combined exposures to higher temperatures and air pollutant concentrations, data on smoking habits, preexisting respiratory and cardiovascular diseases, diabetes, working practices, medications, and exercise habits may be required to explain the differences in response between males and females in similar age groups. Laboratory studies that examine heat stroke as a result of combined exposures to high $T_{\text{max}}$ and NO$_2$ concentrations in both young and older laboratory animals could provide important information on response mechanisms and on how circulating levels of pyrogenic cytokines and heat shock proteins are affected as a result of these combined exposures. Other diseases that also must be examined because the number of emergency transport cases may be affected by increasing surface air temperatures and air pollutant concentrations include cardiovascular diseases such as hypertension, angina, myocardial infarction, and cardiac insufficiency; cerebrovascular diseases such as cerebral hemorrhage, cerebral ischemia, and cerebral infarction; and respiratory diseases such as pneumonia and asthma.

Finally, for reducing the daily number of heat stroke cases, the relationship between higher sea surface temperatures in the equatorial Pacific Ocean in Niño region 3.4 and surface air temperatures in Tokyo must be examined in greater detail. There appears to be a possible relationship between when abnormally high sea-surface temperatures occur in this region of the Pacific Ocean, when abnormally high air temperatures occur in Tokyo, and when abnormally high numbers of emergency transports for heat stroke for the elderly occur in Tokyo.

REFERENCES AND NOTES

1. Houghton JT, Meira Filho LG, Bruce J, Lee H, Gallander BA, Harris N, Kattenberg A, Mackell K. Climate Change 1995: The Science of Climate Change. Contribution of Working Group I to the Second Assessment Report of the Intergovernmental Panel on Climate Change (IPCC). Cambridge, UK: Cambridge University Press, 1996.

2. Michalak AJ, Ando M, Carsenvallo R, Epstein P, Haines A, Jendrasky G, Kalkstein L, Kovats S, Ondoro R, Patz J, et al. Climate Change and Human Health. Geneva: World Health Organization, 1996.

3. Ministry of Health and Welfare. Demographics of Japanese Cities, 1975/1995. Tokyo: Statistics and Information Department, 1997.

4. Stedman RG. The assessment of subtropical Part 1: a temperature-humidity index based on human physiology and clothing science. J Appl Meteorol 18:861–873 (1979).

5. McCullagh P, Neider JA. Generalized Linear Models. London: Chapman and Hall, 1989.

6. Box GEP, Jenkins GM, Reinsel GC. Time Series Analysis: Forecasting and Control. 3rd ed. Englewood Cliffs, NJ: Prentice-Hall, 1994.

7. Lipitz SR, Fitzmaurice GM, Grav EJ, Laird NM. Performance of generalized estimating equations in practical situations. Biometrics 50:270–278 (1994).

8. Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. Am J Epidemiol 132:1136–1141 (1990).

9. SAS Institute, Inc. SAS/STAT Software: Changes and Enhancements through Release 6.12. Cary, NC: SAS Institute, Inc., 1997.

10. Demette JE, O’Mara K, Buurhzer J, Whitney CG, Forzyth S, McNamara T, Adiga RB, Nukuwu MM. Near-fatal heat stroke during the 1995 heat wave in Chicago. Ann Intern Med 129:172–181 (1998).

11. Bouchama A, Al-Sedairy S, Siddiqui S, Shail E, Reznik M. Elevated pyrogenic cytokines in heat stroke. Chest 104:1496–1502 (1993).

12. Burdon RF. Heat shock and the heat shock proteins. Biochem J 240:313–324 (1986).

13. Welch WJ. 1990. The mammalian stress response: cell physiology and biochemistry of stress proteins. In: Stress Proteins in Biology and Medicine (Morimoto R, Tissières A, Georgopoulos C, eds). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1990:223–278.

14. Ando M, Katagiri K, Yamamoto S, Wakahara K, Kawanishi J, Asanuma S, Usuda M, Sasaki K. Age-related effects of heat stress on protective enzymes for paroxysms and microsomal monoxygenase in rat liver. Environ Health Perspect 105:728–733 (1997).

15. Spengler JD, Ferris BG Jr, Dockery DW, Speizer FE. Sulfur dioxide and nitrogen dioxide levels inside and outside homes and the implications on health effects research. Environ Sci Technol 13:1276–1280 (1979).

16. Spengler JD, Duffy CP, Leitz R, Tibottis TW, Ferris BG Jr. Nitrogen dioxide inside and outside 137 homes and implications for ambient air quality standards and health effects research. Environ Sci Technol 17:164–168 (1983).

17. Speizer FE, Ferris BG Jr, Bishop YMM, Speijler J. Respiratory disease rates and pulmonary function in children associated with NO$_2$ exposure. Am Rev Respir Dis 121:13–10 (1980).

18. Ferris BG Jr, Dockery DW, Ware JH, Speizer FE, Spiro R III. The six-city study: examples of problems in analysis of the data. Environ Health Perspect 52:115–123 (1983).

19. Ware JH, Dockery DW, Spiro A III, Speizer FE, Ferris BG Jr. Passive smoking, gas cooking, and respiratory health in children. Am Rev Respir Dis 129:366–374 (1984).

20. Bekebey CS, Ware JH, Dockery DW, Ferris BG Jr, Speizer FE. Air pollution and pulmonary function growth in preadolescent children. Am J Epidemiol 123:250–260 (1986).

21. Guacanboso JJ, Speijler JD, Kanarek MS, Letz R, Duffy CP. Personal exposure to nitrogen dioxide: relationship to indoor/outdoor air quality and activity patterns. Environ Sci Technol 20:775–783 (1986).

22. Dockery DW, Speizer FE, Strom DG, Ware JH, Speijler JD, Ferris BG Jr. Effect of inhalable particles on respiratory health in children. Am Rev Respir Dis 129:567–594 (1989).

23. Naas LM, Dockery DW, Ware JH, Speijler JD, Speizer FE, Ferris BG Jr. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. Am J Epidemiol 134:204–219 (1991).

24. WHO. Nitrogen Oxides. 2nd ed. Environmental Health Criteria Document No. 189. Geneva: World Health Organization, 1997.

25. Kilbourne EM, Keewhan C, Jones TS, Thacker SB. Risk factors for heatstroke. A case-control study. J Am Med Assoc 247:3323–3326 (1982).

26. Jones TS, Liang AP, Kilbourne EM, Griffin MR, Patriarch PA, Wassall SFG, Mullan RJ, Herrick RF, Donnell HD, Choi K, et al. Morbidity and mortality associated with the July 1980 heat wave in St. Louis and Kansas City, Mo. J Am Med Assoc 247:3327–3331 (1982).

27. Climate Analysis Section, University Corporation for Atmospheric Research. Data of Sea-Surface Anomalies in Niño Region 3.4. Available: http://nic.bf.nosoa.gov/data/cdcb/cdcb/sstoi/indices (cited 5 April 1999).