

## **B-10.1.2 Impacts of Global Warming on Human Morbidity**

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### **ABSTRACT**

The daily numbers of heat stroke emergency transport cases/million residents for Tokyo were obtained for males and females in three age groups, 0-14, 15-64 and 65+, for the months of July and August, 1980-1995. The daily numbers of heat stroke emergency transport cases/million residents for each gender and age group were merged with daily average heat index (HI) and concentrations of NO<sub>2</sub> and O<sub>3</sub>. Lag times of 0 (same day) to 4 days in these variables were incorporated into the model as additional risk factors.

Generalized linear models (GLM's) assuming a Poisson error structure, were used to determine if HI, concentrations of NO<sub>2</sub> and O<sub>3</sub>, age, gender and interactions among all of these variables were significant risk factors for heat stroke. To account for correlations among observed daily heat stroke cases from the same sub population group, GLM's were fit using the generalized estimating equation (GEE) method. Responses between males and females and responses by age groups were compared. Same day, or zero lag time HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> were all significant risk factors for heat stroke in all age groups of males and females. A 1-day lag time for HI and NO<sub>2</sub> concentrations and a 2-day lag time for O<sub>3</sub> concentrations were also significant risk factors for all age groups of males and females. Interaction terms for 0- and 1-day lag times in HI and gender in all age groups, and 0-lag time HI and 0-lag time O<sub>3</sub> concentrations and gender in all age groups were additional significant risk factors for heat stroke. 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 0-14 males and females and the greatest number of heat stroke emergency transport cases/million residents occurred for 65+ males and females.

To evaluate the health effects caused by heat stress in summer, regression analysis was carried out between emergency transport data, climatic data, and air pollution. Generalized linear regression models were used to examine heat stroke as functions of average daily temperature, relative humidity, heat index (HI) temperature (a combination of daily temperature and relative humidity) and air pollution concentrations. Best models were obtained when lag time between when exposure occurred and when emergency transport was reported, was either zero or 1 day and when HI temperature was used. Using regression models that contained HI temperature and concentration of NO<sub>2</sub> and O<sub>3</sub>, for males and

females in all age groups, log likelihood tests indicated that HI temperature was a significant factor for heat stroke. For all males and females with a lag time of one day, NO<sub>2</sub> was a significant contributing factor for heat stroke. For all females with a zero lag time, O<sub>3</sub> was a significant contributing factor for heat stroke.

## INTRODUCTION

The Intergovernmental Panel on Climate Change (IPCC) has projected that atmospheric concentrations of CO<sub>2</sub> could double in the next 50 to 100 years (1). Because of the greenhouse effect, a doubling of atmospheric concentrations of CO<sub>2</sub> could result in an increase in global surface temperatures of 1 to 3 °C. In addition, because approximately 65% of atmospheric concentrations of CO<sub>2</sub> are from the combustion of fossil fuels, increasing concentrations of CO<sub>2</sub> could also be accompanied by increasing concentrations of air pollutants, particularly in large urban areas. An increase in surface temperatures could be accompanied by a greater frequency and duration of heat waves, characterized by higher temperatures, higher relative humidities and higher air pollutant concentrations in summer months. Because there could be a greater frequency and duration of heat waves, especially in large metropolitan areas, there could be an increase in the incidence of heat related morbidity and mortality (2).

Periods of prolonged high temperatures, high relative humidities and high air pollutant concentrations occur most often during the summer months of July and August in Tokyo. During this period, combined exposures to these three factors often occur either at the same time or within a short time of each other. Because the frequency and duration of these events may increase in the future, it is important to determine with presently available data the extent to which some or all of these meteorological and air pollutant variables contribute to heat related morbidity, particularly heat stroke, in Tokyo during the summer months of July and August. In addition, the impacts on different age groups of males and females as a result of these combined exposures need to be determined.

## OBJECTIVES

To assess the health effects of global warming, it is necessary to evaluate the threshold temperature and susceptibility for residents. The studies determined that the number of heat stroke emergency transport cases/million for Tokyo during the summer months of July and August, 1980-1995 increased as a result of combined exposures to higher daily maximum temperatures, T<sub>max</sub>, and concentrations of NO<sub>2</sub> and O<sub>3</sub>. Maximum daily temperatures and air pollutant concentrations may increase in Tokyo as a result of climate change. As a result, it is important to determine if temperature and air quality conditions during the warm summer months of July and August in Tokyo are also risk factors for heat stroke.

## METHODS

Data on emergency transport cases for heat stroke for four large medical centers were obtained from medical records compiled by the Tokyo Emergency Office. Daily total numbers of heat stroke emergency transports to hospitals within the city limits of Tokyo for the summer months of July and August, 1980-1995 were stratified by age and gender. The international disease code for heat stroke is 350. Data were obtained in three age groups of males and females; 0-14, 15-64 and 65+.

Yearly average 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 collected by the Ministry of Health and Welfare. 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 about 50% male and 50% female. However, the percentage of residents in the 65+ age group has increased and the percentage of residents in the 0-14 age group has decreased. Data were not available to subdivide the 15-64 age group further, but the percentage of residents in this age group has 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. Comparison of interpolated values to observed values indicated close agreement.

From 1980 to 1995, 85% of the heat stroke emergency transport cases (2060 cases of a total of 2422) occurred either in July or August. The annual average July-August number of heat stroke emergency transport cases/million residents from 1980 to 1995 are shown for males and females in Figures 1 and 2. These graphs indicate that the number of heat stroke emergency transport cases/million residents are greater for males than for females for the same age groups, and that the number of heat stroke emergency transports/million residents are greatest for 65+ males and females. In many instances, the number of heat stroke emergency transport cases/million residents in 15-64 males were almost as high as for 65+ males. High numbers of heat stroke emergency transport cases/million residents for 15-64 and 65+ males and 65+ females were observed in 1987, 1990 1994 and 1995. In addition, the number of heat stroke emergency transport cases/million residents appeared to be increasing for 15-64 males and 65+ males and females after 1993. These results suggested that the number of heat stroke emergency transport cases should be compared by gender and age.

Figures 3 and 4 show the frequency of occurrence of heat stroke in the three age groups of males and females for July-August 1980 to 1995. For most days, there were zero emergency transport cases for heat stroke in all age groups of males and females. This indicated that the daily number of heat stroke emergency transport cases for each age group of males and females were rare and we assume that they are Poisson distributed.

Citywide daily data on air pollutant concentrations, and meteorological variables were obtained from the Japan Environment Agency. Daily 24 hour averages for each weather and air pollutant variable were used rather than peak or maximum daily values because the data were pooled average hourly measurements from four different locations within the city. From these records, daily averages were calculated for NO<sub>2</sub> concentrations, ppb, Oxidant concentrations, ppb; PM<sub>10</sub> concentrations (particles with mean diameters  $\leq 10$   $\mu$ m), (mg/m<sup>3</sup>); air temperatures, T<sub>av</sub>, (°C) and, relative humidity (RH), (percent).

In preliminary analyses of risk factors for heat stroke, it was determined that heat index (HI) was a more significant risk factor for heat stroke than either T<sub>av</sub> or a linear combination of T<sub>av</sub> and RH. Daily average HI combines daily average temperature along with daily average relative humidity in a formula obtained from Arhens (3). HI is not a temperature because it combines air temperature with relative humidity, even though HI is often expressed in units of temperature. Also, the HI is only valid and can only be used when daily average temperatures exceed 21°C. Below 21°C, HI is equal to T<sub>av</sub>.

Figure 5 shows monthly average concentrations for NO<sub>2</sub>, Oxidant, PM<sub>10</sub> and HI from 1980 to 1995. For Tokyo, about 80 to 85% of oxidant concentrations were composed of O<sub>3</sub>. Therefore, O<sub>3</sub> was used throughout this study as the surrogate for oxidant concentrations. Average monthly data for all 12 months of the years from 1980 to 1995 are shown in Figure 5 in order to show the cyclical characteristics of monthly average concentrations of NO<sub>2</sub>, O<sub>3</sub>

and PM10, and HI. The gap in data for PM10 concentrations in 1983 was the result of data being unavailable for a 6 month period during that year. Uno et al (4) reported that concentrations of NO<sub>2</sub> were usually greater in winter months than in summer months. The data in Figure 5 for NO<sub>2</sub> confirm these observations. It is also important to note that in general, average monthly concentrations of NO<sub>2</sub> and PM10 are higher in winter months than in summer months. The highest concentrations of O<sub>3</sub> occur during spring months and the lowest concentrations occur in winter months.

Correlations of all combinations of HI and air pollutant variables indicated that NO<sub>2</sub> and PM10 were moderately collinear,  $r^2 = 0.35$ . To determine which one of these variables should be used in the analysis of heat stroke, linear regression analyses of heat stroke as functions of only NO<sub>2</sub>, of only PM10 and the linear combination of NO<sub>2</sub> and PM10 were carried out. Results of these model studies indicated that PM10 concentrations were not significant contributing factors for heat stroke for both males and females in any age group whereas concentrations of NO<sub>2</sub> were. As a result, PM10 concentrations were not considered further as a risk factor for heat stroke.

The monthly averages for HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> for July and August, 1980 to 1995 are shown in Figure 6. Each of variables for HI and concentrations NO<sub>2</sub> and O<sub>3</sub> appears to be auto correlated and this was taken into account in model development.

The number of heat stroke emergency transports for each day was determined for each age group of males and females and merged with daily averaged NO<sub>2</sub> and O<sub>3</sub> concentrations and HI. The daily number of heat stroke emergency cases/million for the three age groups of males and females were then pooled so that responses between males and females and among the three age groups could be compared for the same daily set of HI and concentrations of NO<sub>2</sub> and O<sub>3</sub>. The beginning location of individual emergency transport cases for heat stroke was not examined in this study because, as indicated earlier, temperature and air pollutant concentration data were used as combined daily averages for the entire metropolitan area of Tokyo and were not location specific.

Generalized linear models (GLM's) were used to determine if HI, concentrations of NO<sub>2</sub> and O<sub>3</sub>, age and gender were significant risk factors for heat stroke (5). It was possible that exposures to high HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> on previous days could affect the number of heat stroke emergency transport cases. To account for this situation, lag times of 0 (same day) to 4 days in the times series for each of these variables were incorporated into the model. A GLM was used instead of an auto-regressive-integrated-moving-average (ARIMA) time series model (6). The rare number of daily heat stroke emergency transport cases made a Poisson distribution more appropriate than a normal distribution. Also, it was not necessary to consider seasonal effects because only data for July and August were used

To determine if age, gender, HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> were important contributing factors for heat stroke, the responses in males were compared to the responses in females, and the responses in the 15-64 and 65+ age groups of males and females were compared to the responses in 0-14 males and females. This type of "reference group" structure is likely to result in correlations between the six sub populations on the number of heat stroke emergency transport cases on any of the 62 days (July-August) of each year. To account for these correlations, GLMs were fit using a generalized estimating equations (GEE) (7, 8). The GLM also made it possible to include interaction terms among HI, concentrations of NO<sub>2</sub> and O<sub>3</sub> with lag times of 0 to 4 days as possible risk factors for heat stroke.

To facilitate numerical accuracy in the regression, HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> were centered by subtracting the overall means for these covariates from their daily

average values. Regression analyses were carried out with SAS software using the GENMOD procedure (9).

## RESULTS AND DISCUSSION

The results indicated that HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> with 0 (same day) lag times were all significant risk factors for heat stroke in all age groups of males and females. Males had a higher risk of heat stroke than females in all age groups. The smallest number of heat stroke emergency transport cases occurred for 0-14 males and females and the greatest number of cases occurred for 65+ males and females. Other risk factors that were specific to all age groups of males and females or to all age groups of males only included: a). HI with a 1 day lag - all age groups of males and females; b). NO<sub>2</sub> concentrations with a 1 day lag - all age groups of males and females; c). O<sub>3</sub> concentrations with a 2 day lag - all age groups of males and females; d). an interaction term for HI temperature with a 0 lag - males in all age groups; e). an interaction term for HI temperature with a 1 day lag - males in all age groups; and, f). an interaction term for HI temperature and O<sub>3</sub> with 0 day lags - all age groups of males and females. Because of its p-value, it could be argued that concentrations of NO<sub>2</sub> with 0 lag time should not be included as a risk factor. However, because NO<sub>2</sub> concentrations with a 1-day lag were significant, concentrations of NO<sub>2</sub> with a 0 lag time were left in the model.

A general regression formula for the rate of heat stroke for each age group of males and females is given as:

$$\text{HS} = \exp[a + b*(\text{HI}) + b*(\text{HI-1day}) + b*(\text{NO}_2) + b*(\text{NO}_2\text{-1day}) + b*(\text{O}_3) + b*(\text{O}_3\text{-2day}) + b*(\text{HI*O}_3)] \quad (1)$$

where the intercept, *a* includes additional terms for males, designated as Gender\_M and age, designated as Age\_65+ and Age\_15-64; *b* is the slope of the term for HI and includes an interaction term for HI and males, designated as HI\_M; *b* is the slope for HI with a 1 day lag, and includes an interaction term for males, designated as HI-1day\_M; and, *b*, *b*, *b*, *b* and *b*, are the slopes for other terms in the model and are the same for all age groups of males and females.

The relationship between combined exposures to higher temperatures and air pollutant concentrations and the physiology and biochemistry of heat stroke is not entirely clear. Heat stroke occurs as a result of heat stress which is the body's response to increasing ambient temperatures. During heat stress, increasing ambient temperatures, causes core body temperature to increase. As core body temperature increases, cardiac output increases and causes more blood flow to be directed to the skin in order to maximize heat removal by conductive, convective and radiation modes of heat transfer (10, 11). As ambient temperatures continue to increase, sweat glands are activated to increase the rate of body heat removal by evaporative heat transfer. In addition, heat shock proteins are synthesized in order to protect vital cells, tissues and organs from thermal damage (12-14). As core body temperature continues to increase, however, blood flow is directed away from the skin in order to maintain blood pressure homeostasis. Core body temperatures continue to increase as ambient temperatures increase and heat stroke occurs.

Older males and females may be more vulnerable to heat stroke than younger males and females for many reasons, many of which are related to aging, level of activity and health status. Increases in blood flow to the skin and the volume of sweat produced as core

body temperatures increase are much less for older males and females than for younger males and females (15). As a result, the capacity of many older males and females to remove increasing body heat is greatly reduced making them more vulnerable to heat stroke at lower ambient temperatures than are younger males and females. With regard to the synthesis of heat shock proteins, studies in laboratory rats have shown that peroxidative damage from heat stress induced by exposure to higher temperatures was greater in older male and female rats than in younger male and female rats (16). Peroxidative damage from heat stress 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.

The difference in the number of heat stroke emergency transport cases between older males and females, is an area that has not been studied extensively. It has been suggested that post menopausal women who are on hormone replacement therapy may have lower average core body temperatures than males in the same age group (17). This may make it possible for this group of women to endure greater thermal loading than males in the same age group, but this is unconfirmed.

The biological explanations for the inclusion of concentrations of NO<sub>2</sub> and O<sub>3</sub> as significant risk factors for heat stroke are not as clear as they are for temperatures. There is considerable evidence that exposures to NO<sub>2</sub> and O<sub>3</sub> reduce pulmonary vital capacity in both laboratory animals and in humans (18-24). In studies by Hackney et al (20), exposure to high concentrations of NO<sub>2</sub> and O<sub>3</sub> in humans resulted in a greater incidence of emergency room visits for pulmonary diseases. For people with pre-existing respiratory disease conditions, the daily number of hospital admissions by gender and age was substantially higher than for people without pre-existing respiratory diseases when exposed to the same concentrations of these air pollutants. More complete summaries of the effects of exposures to NO<sub>2</sub> and O<sub>3</sub> and photochemical oxidants on lung function are given by the WHO (25, 26).

From the analysis of heat stroke in Tokyo, it is suggested by these studies that persons with reduced vital capacities and especially elderly people with reduced vital capacities, may not be able to respond as rapidly or as effectively to combined exposures to increasing HI and air pollutant concentrations in a positive and protective manner. In addition, people who must work hard or who play hard during periods of high HI and air pollutant concentrations may be more vulnerable to heat stroke because protective mechanisms may be more rapidly overwhelmed.

## CONCLUSION

The regression formulas make it possible to estimate the number of heat stroke emergency transport cases for each age group of males and females over a wide range of meteorological conditions and air pollutant concentrations. An example of how these formulas can be used is given in Figure 7 in which the number of heat stroke cases per million for 65+ male and female residents is plotted as a function of daily average HI and NO<sub>2</sub> concentrations. Daily average O<sub>3</sub> concentrations are held constant at their overall mean. The graphs illustrate that the number of heat stroke emergency transport cases/million residents increases as a result of increasing NO<sub>2</sub> concentrations and HI, and that the number of heat stroke cases is greater in 65+ males than in 65+ females. In like manner, increases in the number of heat stroke cases in each age group of males and females per degree change in

HI and per ppb change in concentrations of NO<sub>2</sub> and O<sub>3</sub> can be estimated using the values for model coefficients.

The results suggest that HI, NO<sub>2</sub> and O<sub>3</sub> concentrations, age and gender are all important contributing risk factors for heat stroke in Tokyo during the warm summer months of July and August. Based on the physiology and biochemistry of heat stress, it was expected that the number of heat stroke cases would increase with increasing HI. However, it was unexpected that exposures to NO<sub>2</sub> and O<sub>3</sub> would also be significant contributing risk factors for both males and females in all age groups. Clearly, 65+ males and females are the most vulnerable to the combinations of higher HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> than are younger age groups of males and females. Why the 65+ age group is the most vulnerable and why there are significant differences in response between males and females to high HI and concentrations of NO<sub>2</sub> and O<sub>3</sub> are important areas for additional research.

As indicated above, information on smoking habits and pre-existing respiratory diseases, working practices 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 and heat stress as a result of exposures to high HI, NO<sub>2</sub> and O<sub>3</sub> concentrations in young and aged animals could provide important information on response mechanisms as a result of these combined exposures. Other diseases that need to be examined because the number of emergency transport cases may be affected by temperature and air pollutant concentrations include cardiovascular diseases such as angina, myocardial infarction and cardiac insufficiency, cerebral vascular diseases such as cerebral ischemia and cerebral infarction, and respiratory diseases such as pneumonia and asthma.

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Figure 1. Average annual daily heat stroke rates/1,000,000 for males, 0-14, 15-64 and 65+, Tokyo, July-August, 1980-1995

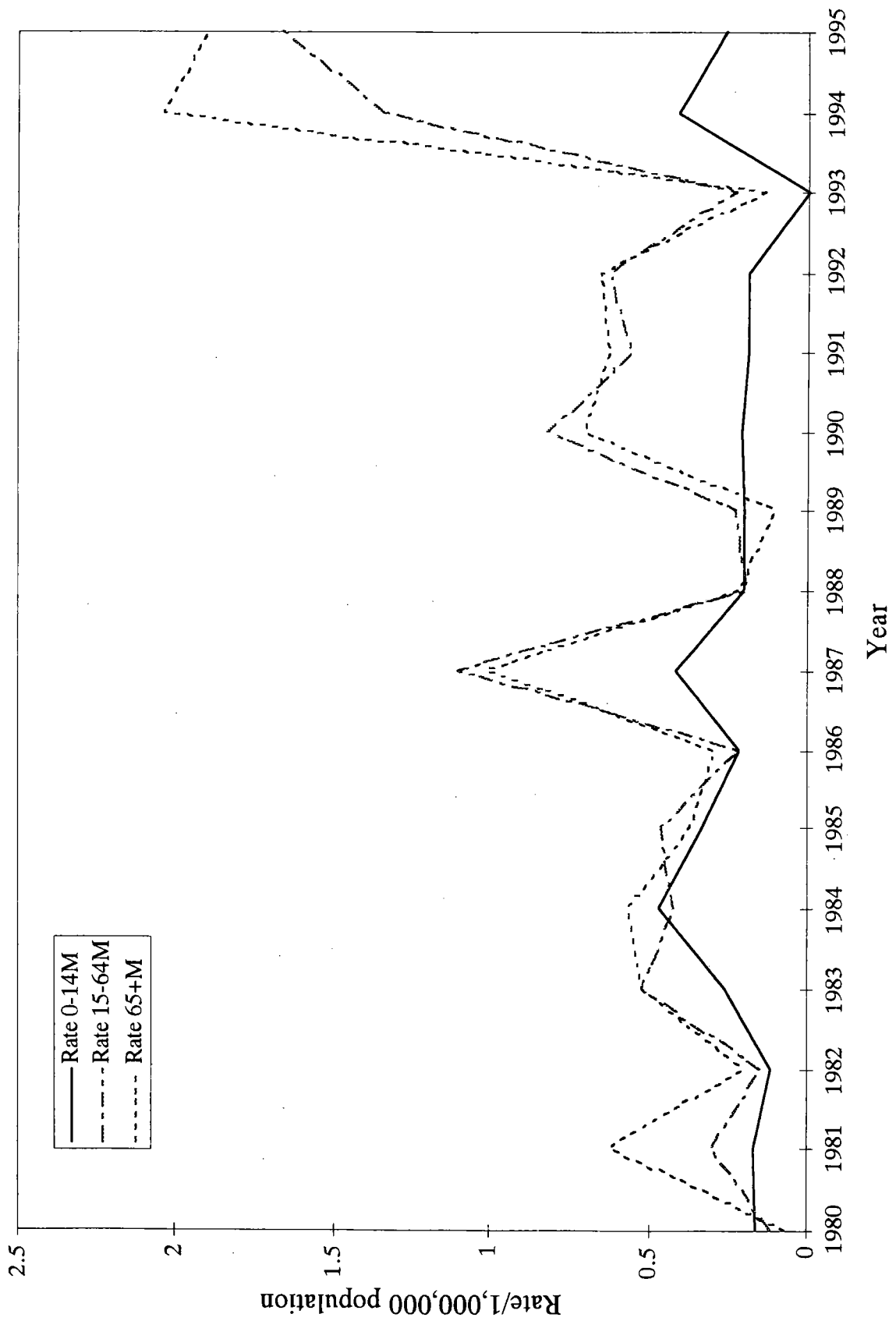


Figure 2. Average annual daily heat stroke rates/1,000,000 for females, 0-14, 15-64 and 65+, Tokyo, July-August, 1980-1995

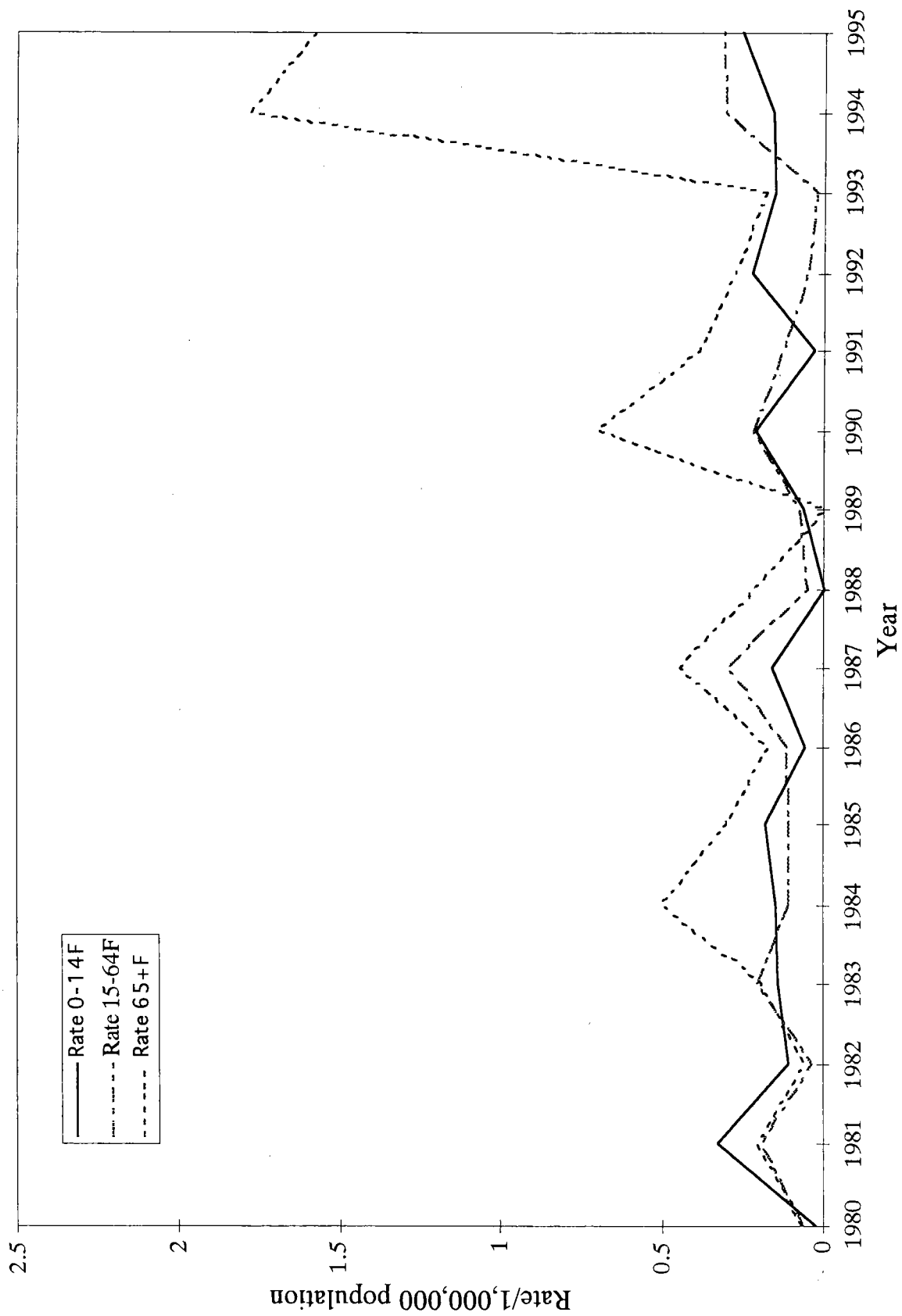


Figure 3. Frequency of occurrence of heat stroke emergency transport cases for 0-14, 15-64 and 65+ males, Tokyo, July-August, 1980-1995

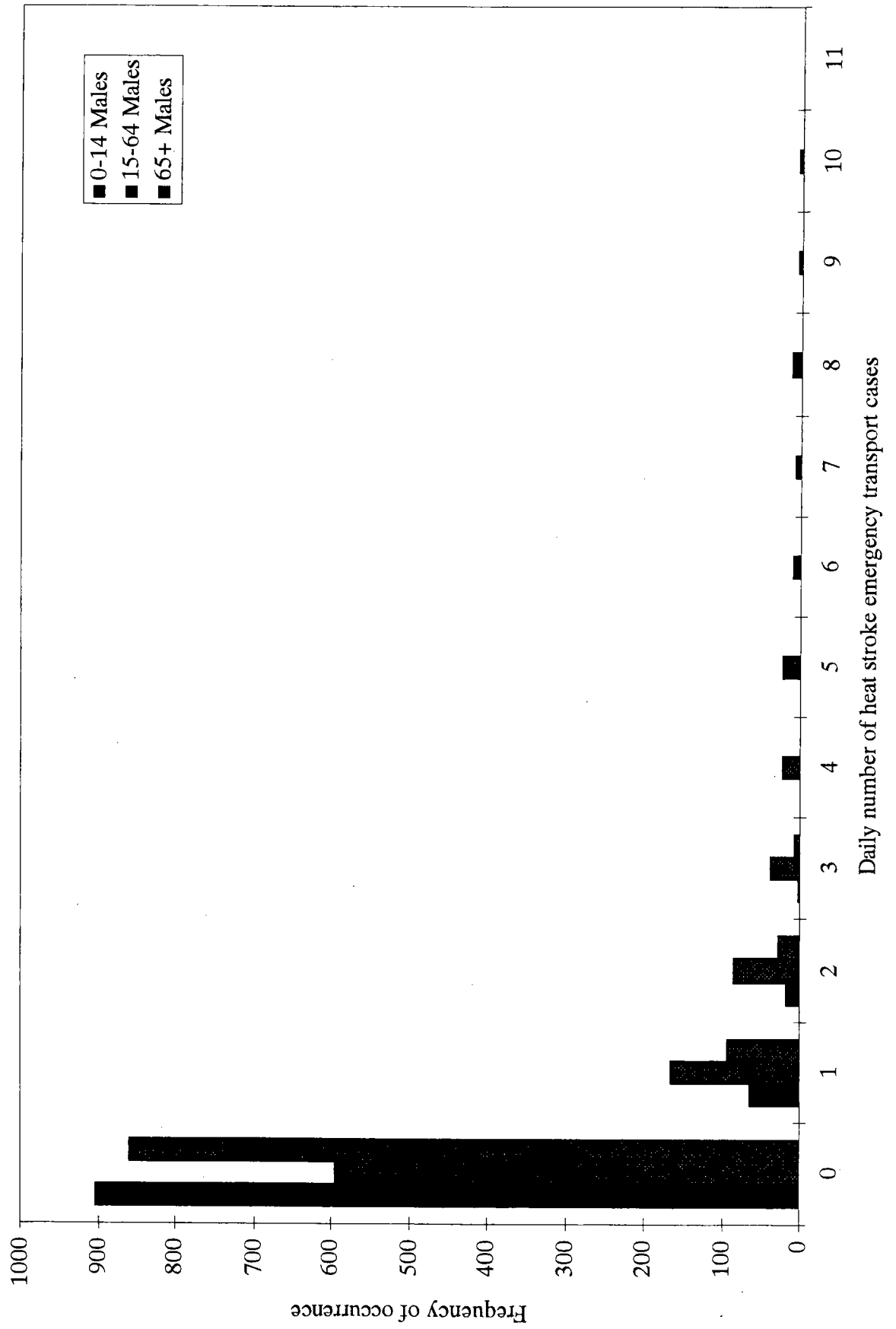


Figure 4. Frequency of occurrence of heat stroke emergency transport cases for 0-14, 15-64 and 65+ females, Tokyo, July-August, 1980-1995

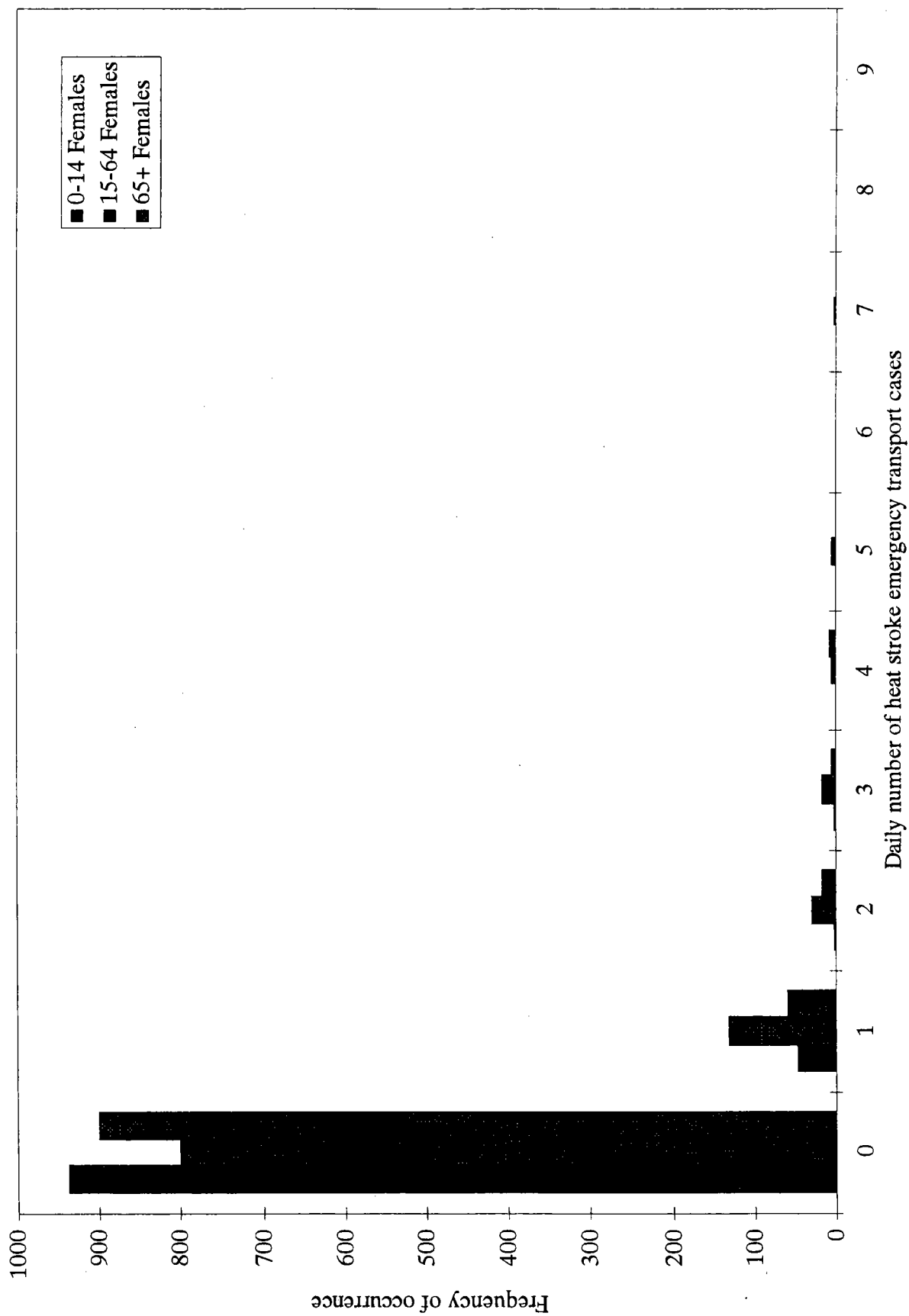


Figure 5. Monthly average concentrations for NO<sub>2</sub>, O<sub>3</sub> and PM<sub>10</sub>, Tokyo, 1980-1995

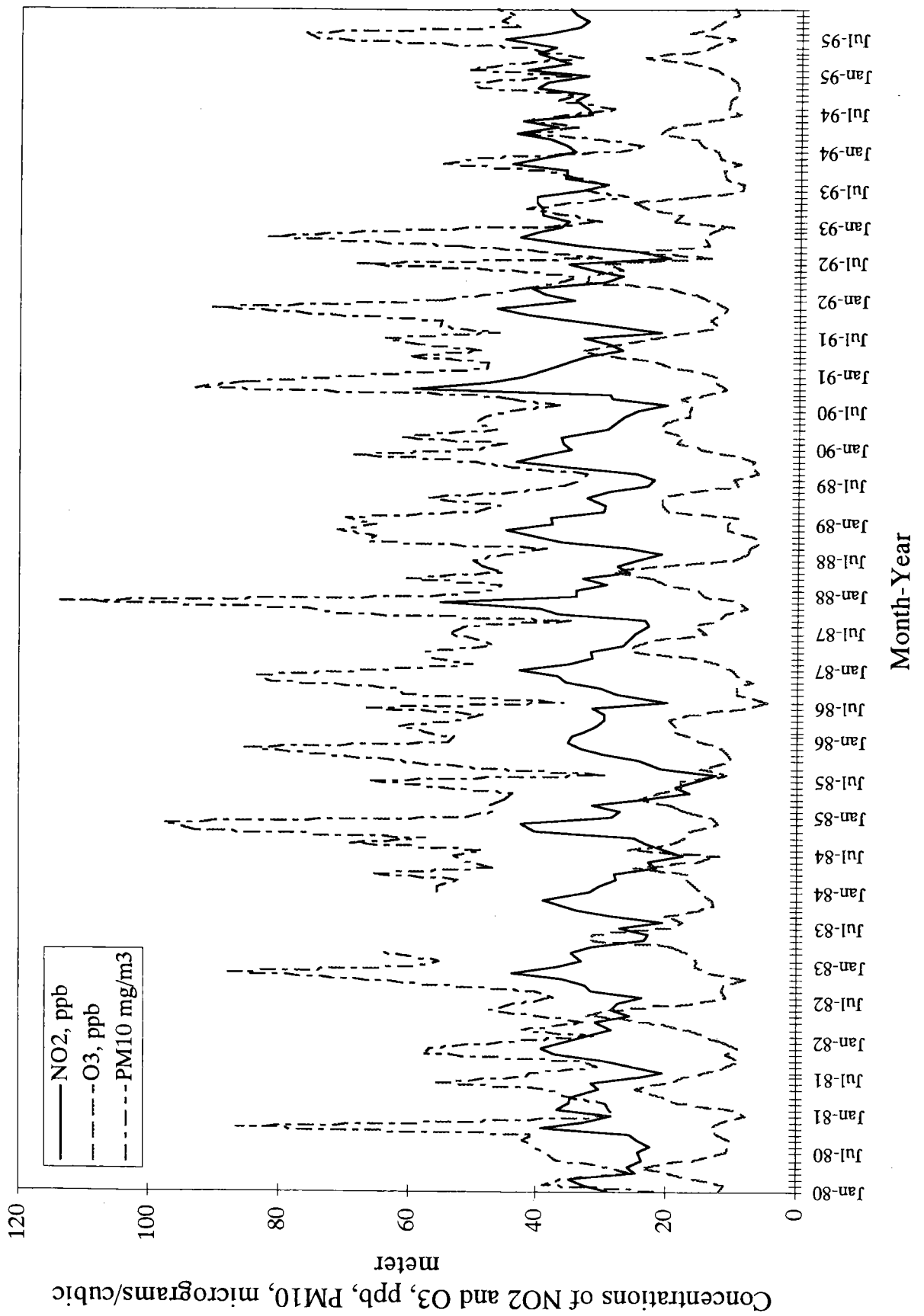


Figure 6. July and August monthly average NO<sub>2</sub> and O<sub>3</sub> concentrations and HI temperatures, Tokyo, 1980-1995

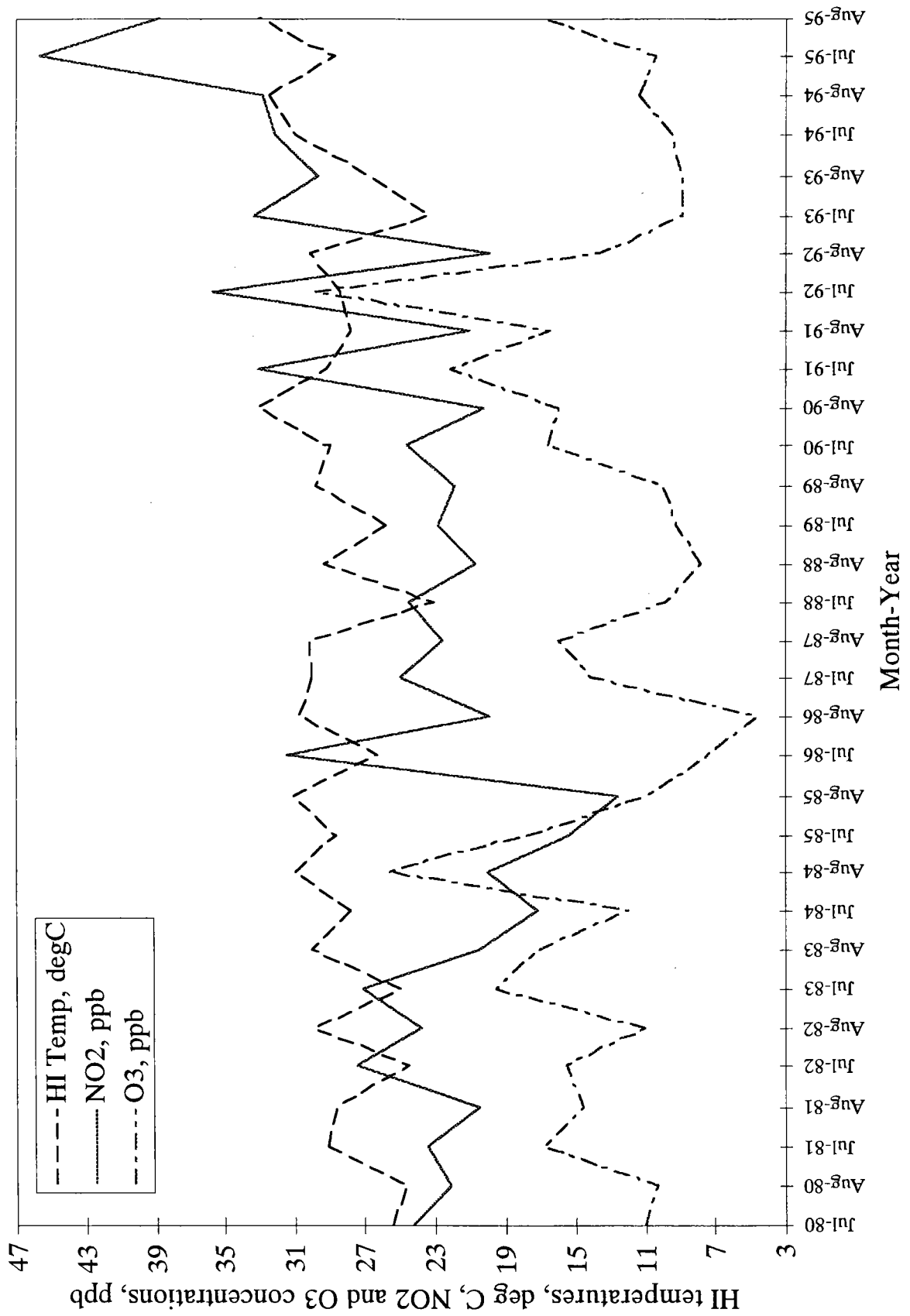
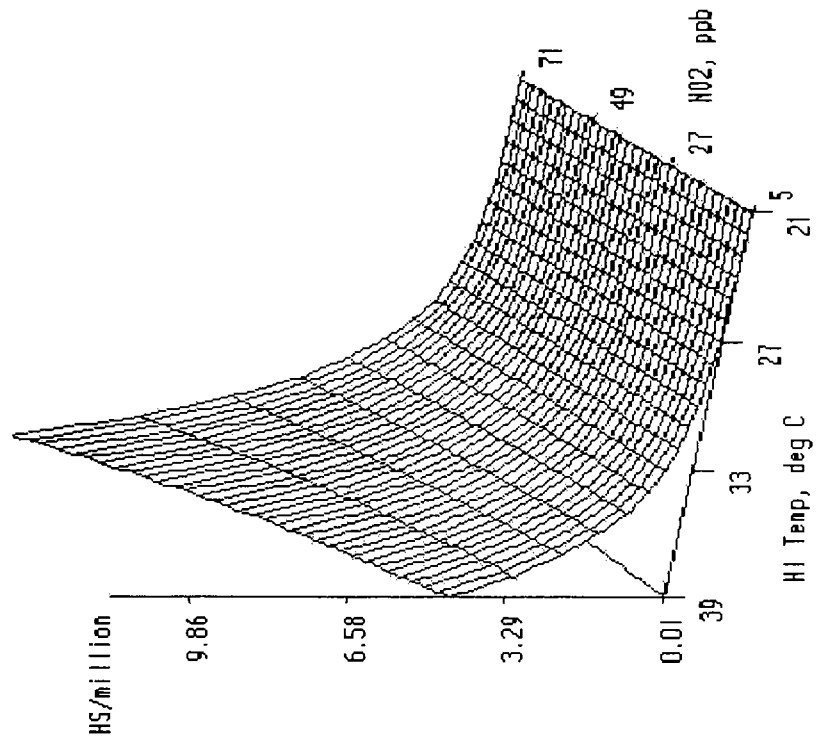


Figure 7. Graphs of regression formulas for the number of heat stroke emergency transport cases/1,000,000 population in 65+ males and females as a function of HI temperatures and NO<sub>2</sub> concentrations, Tokyo, July-August, 1980-1995. O<sub>3</sub> concentrations held constant at mean = 13.9 ppb.

**Males 65+**



**Females 65+**

