## B-10.1.1 Effects of Global Warming on Endcrine Disorders and Preventive Activities to Infection

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**SUMMARY**

Global warming has a potential increase heat stress in hot summer, so various health effects caused by heat stress has been occurred. The epidemiological survey on the incidence of emergency transport cases has been carried out in China and Japan. Heat stress developed immunochemical degeneration in spleen, thymus, lymphatic system, and histochemical change of cellular components in experimental animals. Immune and endocrine disorders, pneumonia and cerebral ischemia have markedly increased in hot temperature. Therefore, global warming may have profound impacts on the immune, endocrine, the defense mechanism for infectious diseases and circulatory systems during heat stress in hot summer.
The bactericidal activity of the lung against *Staphylococcus aureus* is dependent on alveolar macrophages, and that against *Proteus mirabilis* is dependent on alveolar macrophages and polymorphonuclear neutrophils which enter alveoli from the blood. Since pulmonary bacterial clearance against the two types of bacteria was suppressed and the number of alveolar macrophages was reduced, heat must affect phagocytic cells such as, alveolar macrophage and polymorphonuclear neutrophils. The suppression of primary antibody response and pulmonary bacterial clearance, caused by the high-temperature exposure, recovered by removing mice from the high-temperature environment, indicating that this heat-induced suppression is reversible. Furthermore, the effect of the high-temperature exposure on primary antibody response was alleviated by acclimatizing mice at 28°C beforehand, thus confirming that temperature acclimation alleviates the heat-induced suppression in the defense against infections. The results of the present simulation tests on mice suggest that increases in the degree of heat exposure caused by global warming may negatively affect the defense systems against bacterial infections.
Cerebral vascular diseases include cerebral hemorrhage, cerebral infarction and cerebral ischemia. Analysis of the numbers of emergency transport cases/million for these three diseases for July-August, 1980-1995 indicated that 65+ males and females have the highest number of emergency transport cases and the highest frequency of occurrence. Regression models for each disease included maximum daily temperatures, $T_{max}$, and daily average $NO_2$ and $O_3$ concentrations as model co-variates. Generalized linear models (GLMs) and a generalized estimating equation (GEE) method were used to compute estimates of model

parameters.
For cerebral ischemia, same day $T_{max}$, $T_{max}$ with a one day lag time and an interaction term between $T_{max}$ and $O_3$ with a 1 day lag were significant risk factors. The number of emergency transports for cerebral ischemia was slightly greater for males than for females. The underlying mechanisms for these observations may be related to greater heat and air quality stress that can adversely affect cardiovascular and respiratory system functions.

## INTRODUCTION

To assess the process of global warming on human health, it is necessary to combine epidemiological evidences and model experiments in order to predict the future risks. The scenario of global warming is based on Intergovernmental Panel for Climate Change (1996)(1) second assessment reports on climate change. The prediction on mortality rate at community level and vector-borne diseases caused by climate change and ozone depletion has been reported in WHO(1996)(2) and IPCC(1996)(1). According to the IPCC assessment of climate change, it is predicted that global surface temperature will rise between 1°C to 3.5° C by the year 2100. When highest CO2 emission scenario is taken into account, climate model predicts an increase in global mean temperature of 2°C by the year 2040 and 4°C by the year 2100.

It is assessed that temperature rise and change in humidity by global warming will directly affected on heat stress and indirectly influence on ecosystems and environment. The study of excess death in elderly caused by summer heat has assessed that the heat waves will more frequently attack to large cities after global warming. It has been reported that during heat waves when temperature rises above the threshold value, mortality of the residents in the cities remarkably increased. Therefore, global warming may have profound impacts on the immune, endocrine, the defense mechanism for infectious diseases and circulatory systems during heat stress in hot summer.

## OBJECTIVES

For the assessment on the health effects of global warming, it is necessary to accumulate the new evidences because health status in community is important to evaluate the threshold temperature and susceptibility for residents. The studies determined that the number of emergency transport cases of cerebral vascular diseases /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, $T_{max}$, and concentrations of $NO_2$ and $O_3$. 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 cerebral vascular diseases.

## METHODS

The three cerebral vascular diseases that were studied were cerebral hemorrhage, International Disease Code (IDC) = 481, cerebral infarction (IDC = 482) and cerebral ischemia (IDC = 483). Data on emergency transports to four Tokyo city hospitals for these three diseases for the warm summer months of July and August from 1980 to 1995 were obtained from medical records compiled by the Tokyo Emergency Office. Data were

stratified for three age groups of males and females: 0-14, 15-64 and 65+. Initial analysis of these three cerebral vascular diseases indicated, however, that the greatest number of emergency transport cases occurred for 65+ males and females. As a result, analyses of temperature and air pollution risk factors were confined to this age group.

The number of emergency transport cases/million residents for each year in this study was determined from age distribution data obtained from the Ministry of Health and Welfare, Statistics and Information Department in Tokyo. Yearly average numbers of emergency transport cases/million residents for the three cerebral vascular diseases for 65+ males and females for the months of July and August were determined from population data provided 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. The percentage of residents in the 15-64 age group has remained relatively constant from 1980 to 1995. In the development of the regression models for each of the three cerebral vascular diseases, changes in population were taken into consideration for 65+ males and females living in Tokyo from 1980 to 1995.

## RESULTS AND DISCUSSION

Figure 1 graphs the average annual July-August number of cerebral vascular disease emergency transport cases/million for 65+ males and females are plotted. These results indicate that the numbers of cerebral hemorrhage and cerebral ischemia emergency transport cases declined from 1980 to 1995, whereas the numbers of cerebral infarction emergency transport cases increased for this same time period. There did not appear to be a large difference in response between males and females for both cerebral hemorrhage and cerebral ischemia, but for cerebral infarction, the number of emergency transport cases was greater in all years for males than for females.

Figure 2 graphs the daily frequencies of occurrence of these three cerebral vascular diseases for 65+ males and females are plotted. Calculations of means and variances of the density functions for each of these diseases indicated that the density functions for the daily number of emergency transports cases for each of these three cerebral vascular diseases for 65+ males and females could be assumed to be Poisson distributed because of the skewed nature of the count data.

Figure 3 graphs the number of emergency transports for each of the three cerebral vascular diseases for 65+ males and females as a function of daily maximum temperature, $T_{max}$, °C are plotted for the summer months of July and August from 1980 to 1995. The graph indicates that the numbers of emergency transport cases/million for cerebral hemorrhage and cerebral ischemia for 65+ males and females do not appear to be greatly affected by increasing daily maximum temperatures. However, the numbers of cerebral infarction emergency transport cases for 65+ males and females appear to be increasing with increasing temperature. In this initial stage of regression model development, these results suggested that the regression models for each disease needed to be constructed so that response in males could be compared to the response in females. A justification for the construction of regression models based on $T_{max}$ rather than average daily temperatures, minimum daily temperatures or the heat index was that during a heat wave, hot days are an important indicator of high levels of heat stress for the elderly.

To construct regression models for the three cerebral vascular diseases, citywide

daily concentrations of air pollutants and weather variables were obtained from the Japan Environment Agency for the months of July and August from 1980 to 1995. Daily 24 hour averages for each air pollutant variable that was used in these analyses were calculated from pooled hourly measurements from four different measurement locations within the city. Daily maximum temperatures, $T_{max}$, °C, were also obtained from this same data set. From these records, daily averages were calculated for $NO_2$ concentrations, ppb, photochemical oxidant concentrations, ppb; and $PM_{10}$ concentrations, ug/m3. For Tokyo, about 80 to 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.

Correlations of all pairs of co-variates indicated that $NO_2$ and $PM_{10}$ were moderately collinear, $r = 0.59$. To determine which one of these concentrations should be used in the analysis of cerebral vascular diseases, linear regression analyses of each disease as functions of only $NO_2$, of only $PM_{10}$ and the linear combination of $T_{max}$, $NO_2$ and $PM_{10}$ were carried out. Results of these model studies indicated that concentrations of $NO_2$ were more significant contributing risk factors for cerebral ischemia and cerebral infarction. Both concentrations of $NO_2$ and $PM_{10}$ were not significant contributing factors for cerebral hemorrhage. As a result, $PM_{10}$ concentrations were not considered further as an air pollutant risk factor for these three cerebral vascular diseases.

A generalized linear model (GLM), in particular a Poisson regression model, was used to determine which of the co-variates in the regression models for each of the three cerebral vascular diseases were significant risk factors (McCullagh and Nelder, 1989)(6). A GLM was used instead of an auto-regressive-integrated-moving-average (ARIMA) time series model because the number of daily cerebral vascular disease emergency transport cases were Poisson distributed and not normally distributed (Box et al, 1994)(3).

Because it was possible that $T_{max}$, and concentrations of $NO_2$ and $O_3$ on previous days could affect the number of cerebral vascular disease cases in 65+ males and females observed for the present day, lag times of 1 to 4 days for each of these co-variates were incorporated into the model as additional risk factors. Terms to account for interactions among pairs of model co-variates were also included. In addition, daily $T_{max}$ and concentrations of $NO_2$ and $O_3$ were centered by subtracting the overall means for each of these co-variates.

In order to filter out any long term trends that may have occurred from 1980 to 1995, yearly variables were incorporated into the models to account for these annual trends. 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 in each model to account for an increasing population of 65+ males and females in Tokyo from 1980 to 1995. To account for serial correlations, model parameters in the GLMs were fit using a generalized estimating equation (GEE) method (Lipsitz et al, 1994(5); Schwartz, 1993)(10). Regression analyses were carried out with SAS software using the GENMOD procedure (SAS, 1997)(9).

The bactericidal activity of the lung against *Staphylococcus aureus* is dependent on alveolar macrophages, whereas that against *Proteus mirabilis* is dependent on alveolar macrophages and polymorphonuclear neutrophils which enter alveoli from the blood. Since pulmonary bacterial clearance against the two types of bacteria was suppressed and the number of alveolar macrophages was reduced, heat must affect phagocytic cells such as, alveolar macrophage and polymorphonuclear neutrophils.

The suppression of primary antibody response and pulmonary bacterial clearance, caused by the high-temperature exposure, recovered by removing mice from the high-temperature environment, indicating that this heat-induced suppression is reversible. Furthermore, the effect of the high-temperature exposure on primary antibody response was alleviated by acclimatizing mice at 28°C, thus confirming that temperature acclimation alleviates the heat-induced suppression in the defense against infections. The results of the present simulation tests on mice suggest that increases in the degree of heat exposure caused by global warming may negatively affect the defense systems against bacterial infections. However, this can be minimized by avoiding heat exposure or taking appropriate actions.

Based on p-value calculations for significant model parameters, models with $T_{max}$ was a significant risk factor for cerebral hemorrhage and cerebral ischemia in 65+ males and females. For cerebral infarction, only $NO_2$ was a significant air pollution risk factor, and the number of emergency transports for cerebral infarction was greater in males than in females. This result contradicts the observations given in Figure 3, because the number of emergency transport cases/million for cerebral infarction appears to increase slightly with $T_{max}$. However, at that early stage in model development, the primary consideration was to determine which co-variates needed to be considered in the initial model.

For cerebral hemorrhage, $T_{max}$ with a lag time of 4 days was the primary risk factor, and there was no difference in response between males and females. It was not apparent why such a long lag time for $T_{max}$ should be significant rather than same day or lag times of 1 to 3 days for $T_{max}$. For cerebral ischemia, same day $T_{max}$, $T_{max}$ with a one day lag time and an interaction variable between $T_{max}$ and $O_3$ with a 1 day lag were the risk factors. The number of emergency transports for cerebral ischemia was slightly greater for males than for females.

Cerebral vascular diseases cause neurological impairment as a result of vascular brain damage and occur more frequently in the elderly (Munari and Porta, 1990)(7). Acute cerebral vascular diseases are described as a sudden neurologic failure followed by permanent sequelae, coma or death, and are characterized as disorders of inadequate blood supply to brain tissues and cells. Chronic cerebral vascular disease is the result of the accumulation of focal ischemic injuries. Literature citations that examine temperature and air pollution as risk factors for cerebral vascular diseases were not found. However, the results of this investigation suggest that increasing maximum daily temperatures and air pollutant concentrations are risk factors for cerebral hemorrhage and cerebral ischemia for 65+ males and females. By contrast, cerebral infarction appeared to be only a function of $NO_2$ concentrations.

Exposures to higher daily maximum temperatures and air pollutant concentrations may produce additive or synergistic heat and air quality stress conditions for people with cerebral vascular diseases. Further studies on the yearly variability in the numbers of emergency transports/million for these three diseases as functions of daily maximum temperature and air pollutant concentrations may be important to identify seasonal trends in these three cerebral vascular diseases. Hypertension is often sited as a significant risk factor for acute cerebral vascular diseases (Kameyama et al, 1988)(4), and the relationship between hypertension, temperature and air pollution is an area that also appears to require additional study. Finally, it was not possible with the data available for this analysis to determine why there should be a decline in the annual number of emergency transport cases/million for cerebral hemorrhage and cerebral ischemia and an increase in the annual number of emergency transport cases/million for cerebral infarction. In this regard, dietary changes may

be an important contributing factor for reducing the risk of accumulation of focal ischemic injuries.

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Figure 1. Average annual July-August number of cerebral Hemorrhage (CEH), cerebral infarction (CEIN) and cerebral ischemia (CEIS) emergency transport cases/million for 65+ males and females, Tokyo, 1980-1995

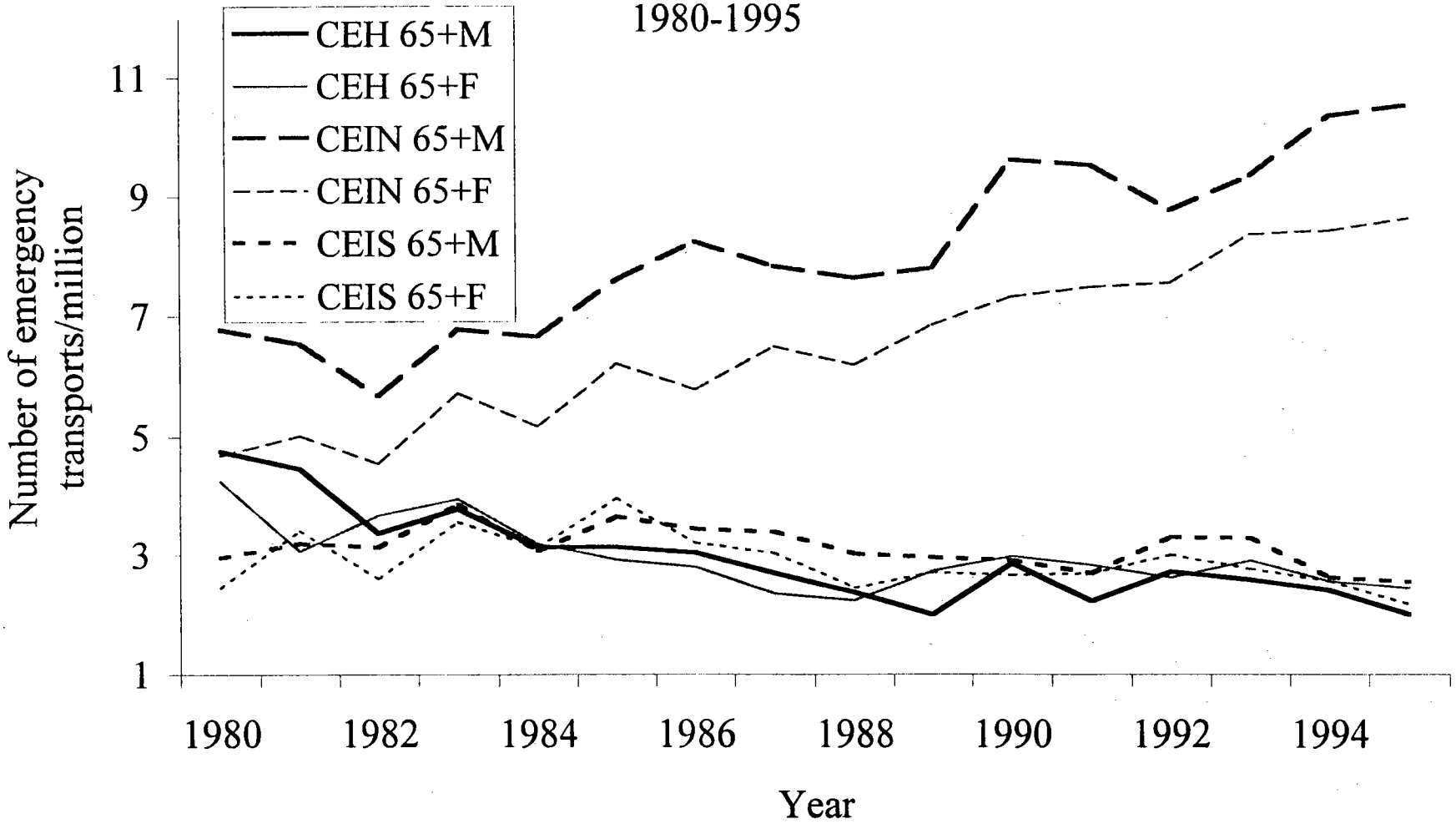

Figure 2. Frequency of occurrence of cerebral hemorrhage (CEH), cerebral infarction (CEIN) and cerebral ischemia (CEIS) for 65+ males and females, Tokyo, July-August, 1980-1995

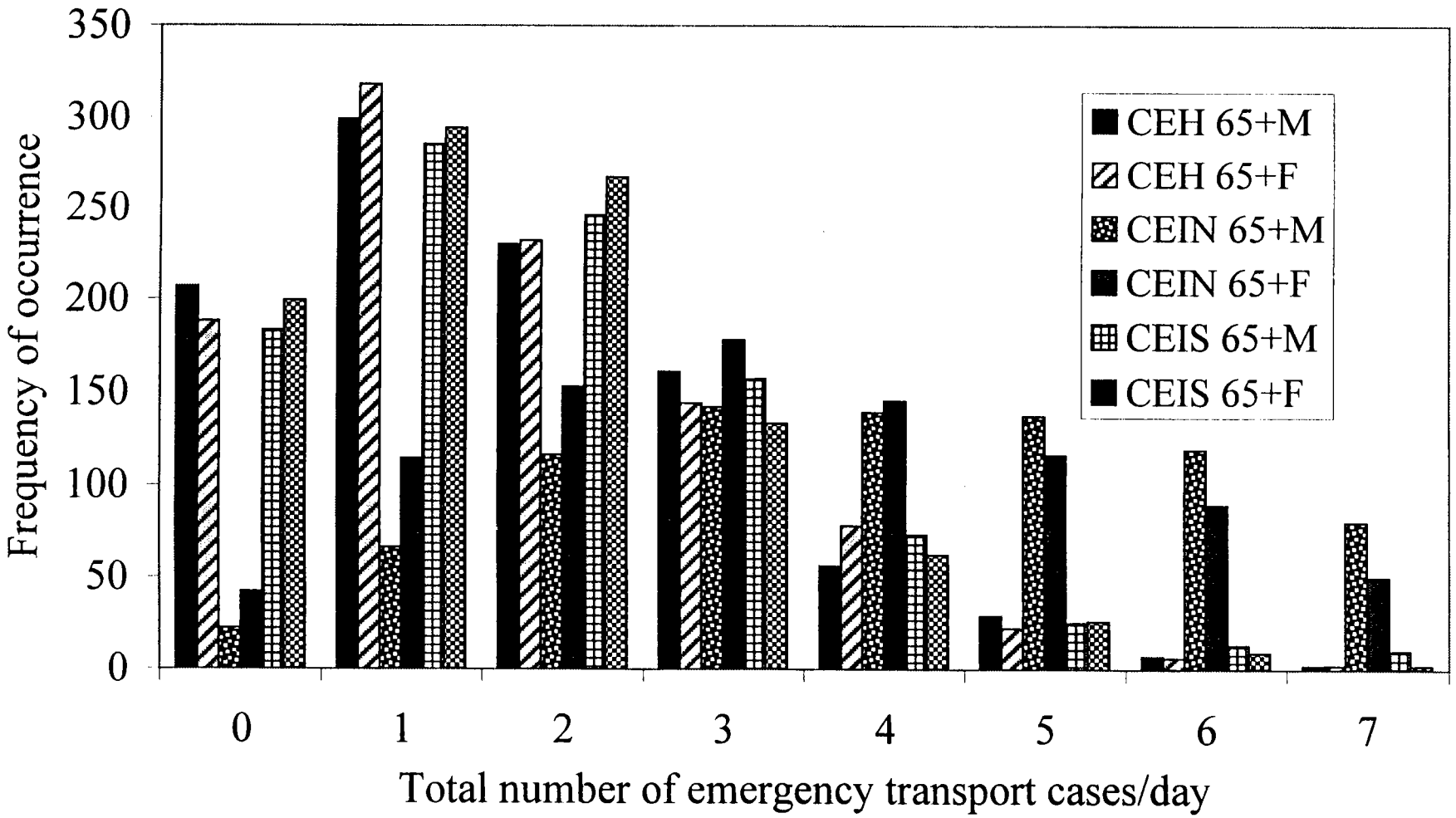

Figure 3. Number of emergency transport cases/million for cerebral hemorrhage (CEH) and cerebral ischemia (CEIS) for 65+ males and females as a function of $T_{max}$, Tokyo, July-August, 1980-1995