

EPIDEMIOLOGICAL FEATURES OF INTRACTABLE DISEASES IN JAPAN: VARIATIONS IN DEATHS BY SEX AND AGE*

YOSHIYUKI OHNO, NOBUYUKI HAMAJIMA,
RYUICHIRO SASAKI and KUNIO AOKI

*Department of Preventive Medicine Nagoya University School of Medicine
65 Tsurumai-cho Showa-ku Nagoya Aichi 466, Japan*

ABSTRACT

Sex differences in deaths from nineteen intractable diseases were devotedly examined by the 95 percent confidence interval for a ratio of male deaths to female deaths in 1977-1980, Japan. Few intractable diseases failed to demonstrate an appreciable difference in frequency between the sexes. What interestingly emerged from the analysis were an obvious female predominance in intractable diseases for which autoimmune mechanisms are presumably incriminated and either male or female predisposition to intractable diseases in which the vascular system is principally affected. Possible etiological implications of different frequency of disease by sex and age were also discussed. Sex- and age-oriented investigations are finally believed to be of extreme importance particularly for intractable diseases.

Key words: Epidemiology, Intractable diseases, Sex, Age

INTRODUCTION

Diseases could be, in general, classified into three categories: those in which males predominate, those in which females do and those with no obvious sex preponderance in occurrence.

Some intractable diseases, which have been defined as such¹⁾ by Ministry of Health and Welfare, Japan, often show the marked differences in frequency between the sexes.

Sex difference in disease frequency is usually measured by sex ratio. Sex ratio is conventionally expressed as a ratio either of sex specific numbers of disease outcome or of age-adjusted rates between males and females.

In this paper, sex difference is examined by its simplest form, a ratio of male deaths to female deaths, for several intractable diseases which mainly affect the vascular system and those for which autoimmune mechanisms are presumably responsible. Distribution patterns of age specific death rates will also be examined by sex for some intractable diseases with available information for analysis.

大野良之, 浜島信之, 佐々木隆一郎, 青木国雄

* This work was in part supported by the grant from Ministry of Health and Welfare of Japanese Government

Received for Publication January 10, 1983

MATERIALS AND METHODS

Sex specific numbers of deaths from 19 intractable diseases were provided from the four reports²⁾ published by Research Council on Epidemiology of Intractable Diseases, which is supported by Ministry of Health and Welfare, Japan. Age and sex specific populations were routinely obtained³⁾ for the study period of 1977-1980.

Diseases selected for an analysis consisted of two defined categories: intractable diseases in which the vascular system is mainly affected and those for which some autoimmune mechanisms are presumed to be responsible. The former included thromboangitis obliterans, cardiomyopathy, primary pulmonary hypertension, juvenile hypertension, polyarteritis nodosa, moyamoya disease and aortitis syndrome; the latter, polyarteritis nodosa, nephrotic syndrome, chronic glomerulonephritis, ulcerative colitis, adrenal insufficiency, multiple sclerosis, autoimmune hemolytic anemia, myasthenia gravis, polymyositis and dermatomyositis, malignant rheumatoid arthritis, thyrotoxicosis, progressive systemic sclerosis and systemic lupus erythematosus. Polyarteritis nodosa was regarded as a disease which might probably belong to both categories.

Sex difference was measured by sex ratio expressed as a ratio of the total number of male deaths to that of female deaths for the study period en bloc. The 95 percent confidence limits for the ratio thus calculated were obtained as described in Appendix.

In brief, let n , p' , and R denote the total number of deaths (male deaths plus female deaths), the proportion of male deaths in total deaths and sex (male to female) ratio, respectively. Then, the 95 percent confidence limits for R are given as

$$\frac{p' - 1.96\sqrt{p'(1-p')/n}}{1 - (p' - 1.96\sqrt{p'(1-p')/n})} \leq R \leq \frac{p' + 1.96\sqrt{p'(1-p')/n}}{1 - (p' + 1.96\sqrt{p'(1-p')/n})}$$

Thus, sex ratio (R) could be determined as significantly different from unity, when this 95 percent confidence interval excludes 1.

Of 19 intractable diseases selected, 11 diseases could be examined by sex as to age specific death rates; populations were averaged for 1977-1978, 1979-1980 and 1977-1980 for this purpose.

RESULTS

Table 1 shows sex specific number of deaths, sex (male to female) ratio and its 95 percent confidence interval for 19 intractable diseases in 1977-1980 in Japan. Those for polyarteritis nodosa are presented twice. Since it was difficult to maintain chronologically the uniform classification of disease simply due to the revised ICD between 1978 and 1979, above information could not readily obtained for 8 diseases throughout the study period of four years. As a consequence, information in 1979-1980 was presented for 7 diseases of cardiomyopathy, primary pulmonary hypertension, moyamoya disease, adrenal insufficiency, chronic glomerulonephritis, autoimmune hemolytic anemia and malignant rheumatoid arthritis; that in 1977-1978 for juvenile hypertension.

Among 19 intractable diseases selected, cardiomyopathy, nephrotic syndrome, chronic glomerulonephritis and systemic lupus erythematosus were rather large in number; two diseases of moyamoya disease and autoimmune hemolytic anemia, by contrast, relatively small in number. These sex specific numbers of deaths were, however, believed to be large enough to yield the stable sex ratio and 95 percent confidence limits.

Table 1 Sex Specific Numbers of Deaths, Sex Ratios and 95 Percent Confidence Limits for Selected Intractable Diseases in 1977-1980, Japan

Diseases (ICD codes)	Numbers of deaths			Sex ratio (M/F)	95% Conf. Int.	
	Total	Males	Females		Lower	Upper
Thromboangitis obliterans (443.1)	192	148	44	3.36	2.46	4.89
Cardiomyopathy (425)*	1348	871	477	1.83	1.64	2.05
Juvenile hypertension (400)**	658	371	287	1.29	1.11	1.51
Polyarteritis nodosa (446.0)	205	112	93	1.20	0.92	1.59
Primary pulmonary hypertension (416.0)*	176	70	106	0.66	0.48	0.89
Moyamoya disease (437.5)*	87	25	62	0.40	0.24	0.62
Aortitis syndrome (446.9A; 446.7)	212	55	157	0.35	0.25	0.47
Polyarteritis nodosa (446.0)	205	112	93	1.20	0.92	1.59
Nephrotic syndrome (581)	1811	898	913	0.98	0.90	1.08
Ulcerative colitis (563.1; 556.0)	800	376	424	0.89	0.77	1.02
Adrenal insufficiency (255.4)*	142	66	76	0.87	0.62	1.21
Chronic glomerulonephritis (582.9)*	4006	1854	2152	0.86	0.81	0.92
Multiple sclerosis (340.0; 340)	293	125	168	0.74	0.59	0.94
Myasthenia gravis (733.0; 358.0)	308	123	185	0.66	0.53	0.83
Autoimmune hemolytic anemia (283.0)*	48	17	31	0.55	0.28	0.96
Polymyositis and dermatomyositis (716.0-1; 710.3-4)	456	153	303	0.50	0.41	0.61
Malignant rheumatoid arthritis (714.2A)*	255	77	178	0.43	0.33	0.56
Thyrotoxicosis (242)	457	106	351	0.30	0.24	0.37
Progressive systemic sclerosis (733.0; 710.0)	533	96	437	0.22	0.17	0.27
Systemic lupus erythematosus (734.1; 710.0)	1798	193	1605	0.12	0.10	0.14

No asterisk: 1977-1980, *: 1979-1980, **: 1977-1978

In Figure 1, sex ratio with 95 percent confidence interval is depicted for 19 intractable diseases in Table 1; polyarteritis nodosa is again presented twice.

Intractable diseases with sex ratio significantly above unity, i.e., those in which males significantly predominated, were thromboangitis obliterans, cardiomyopathy and juvenile hypertension. Diseases with sex ratio significantly below unity, i.e., those in which females significantly outnumbered males, were primary pulmonary hypertension, moyamoya disease, aortitis syndrome, chronic glomerulonephritis, multiple sclerosis, myasthenia gravis, autoimmune hemolytic anemia, polymyositis and dermatomyositis, malignant rheumatoid arthritis, thyrotoxicosis, progressive systemic sclerosis and systemic lupus erythematosus. Diseases with no significant sex preponderance were polyarteritis nodosa, nephrotic syndrome, ulcerative colitis and adrenal insufficiency. Though not included in Table 1 and Figure 1, no deaths in males and twelve deaths in females were ascribed to Hashimoto's disease in 1977-1980 in Japan.²⁾

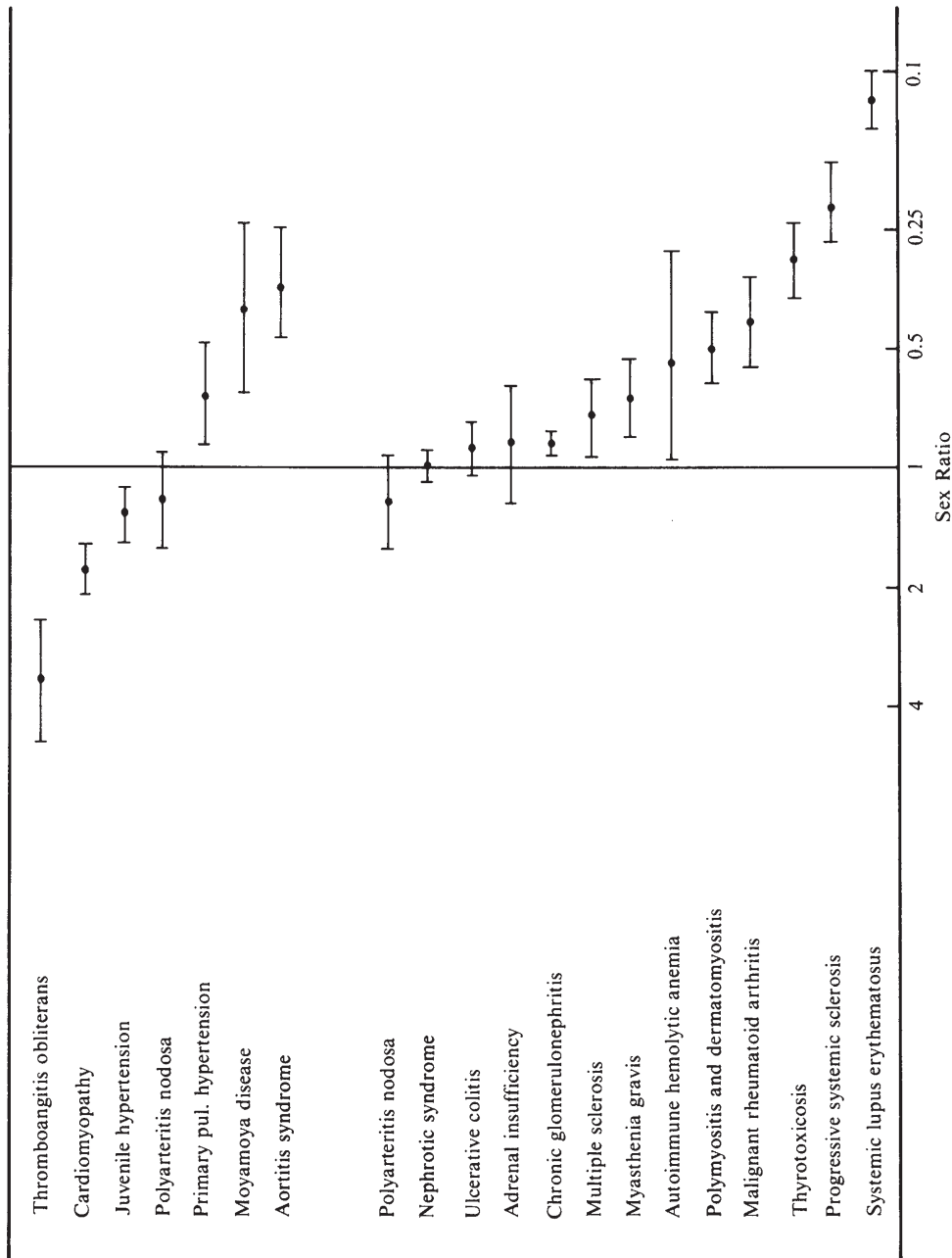


Fig. 1 Graphic Illustration of Sex Ratios with 95 Percent Confidence Limits for Selected Intractable Diseases, Japan

What interestingly emerged from the analysis is, in summary, an appreciable female predominance in intractable diseases for which some autoimmune mechanisms are presumably responsible. By contrast, either male or female predominance is observed in intractable diseases with pathological involvement of the vascular system.

Among 19 intractable diseases, age and sex specific numbers of deaths were available in 11 diseases from the four reports²⁾ and/or mortality statistics in Japan.⁴⁾

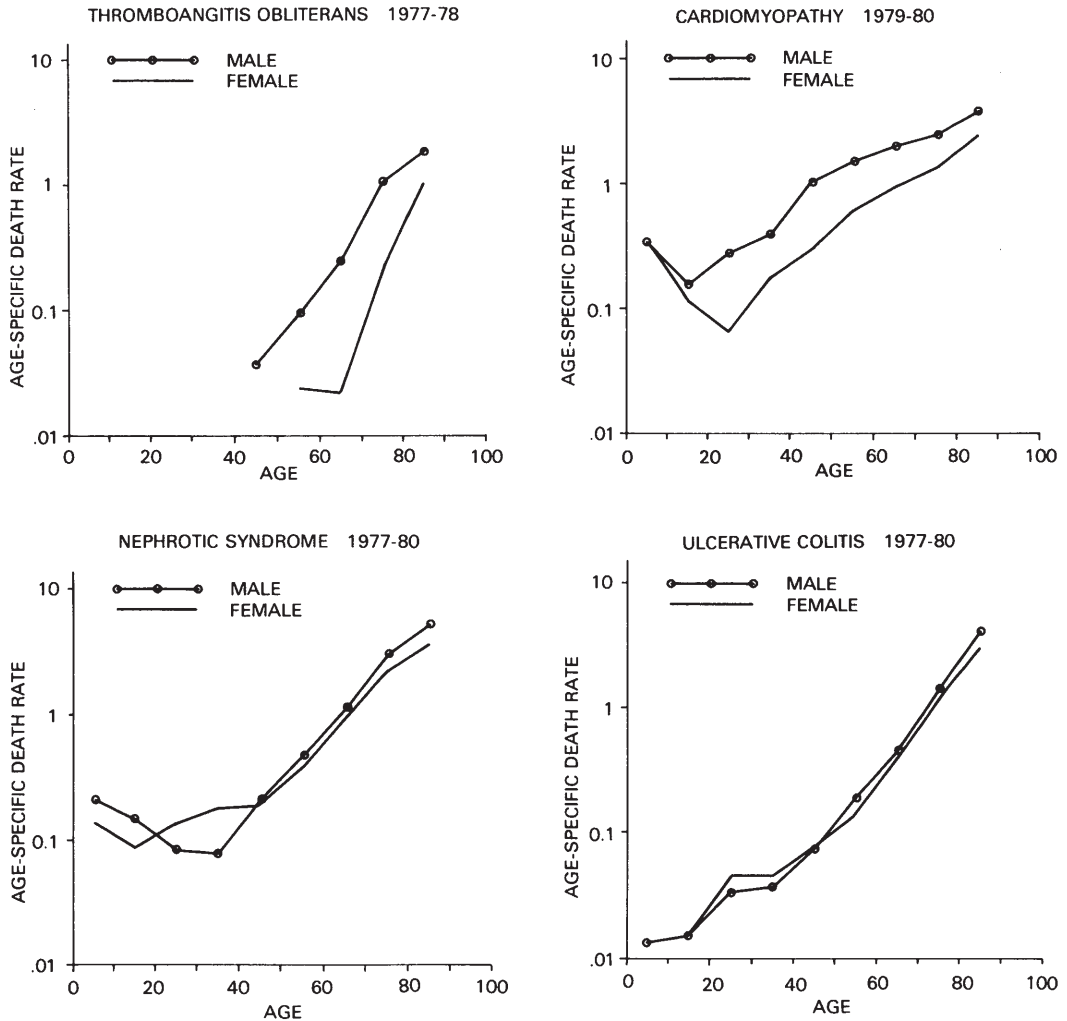


Fig. 2. 1 Distribution of Age Specific Death Rates per 100,000 population by Sex

Distributions of age specific death rates per 100,000 population are illustrated by sex in Figure 2.1-2.3.

In two intractable diseases with sex ratio significantly above unity (thromboangitis obliterans and cardiomyopathy) in Figure 2.1, the death rates increased linearly from approximately 40 years of age up to the extreme ages. Magnitude of sex difference in age specific death rates appeared to decrease with advancing ages. In cardiomyopathy, the death rates were not different by sex under 20 years of age. In these two diseases, male death rates were uniformly higher than female rates in every age group.

In two intractable diseases with insignificant sex ratio (nephrotic syndrome and ulcerative colitis) in Figure 2.1, male and female rates ran quite closely each other after 40 years of age, though age curve was somewhat different by sex below 40 years of age in nephrotic syndrome.

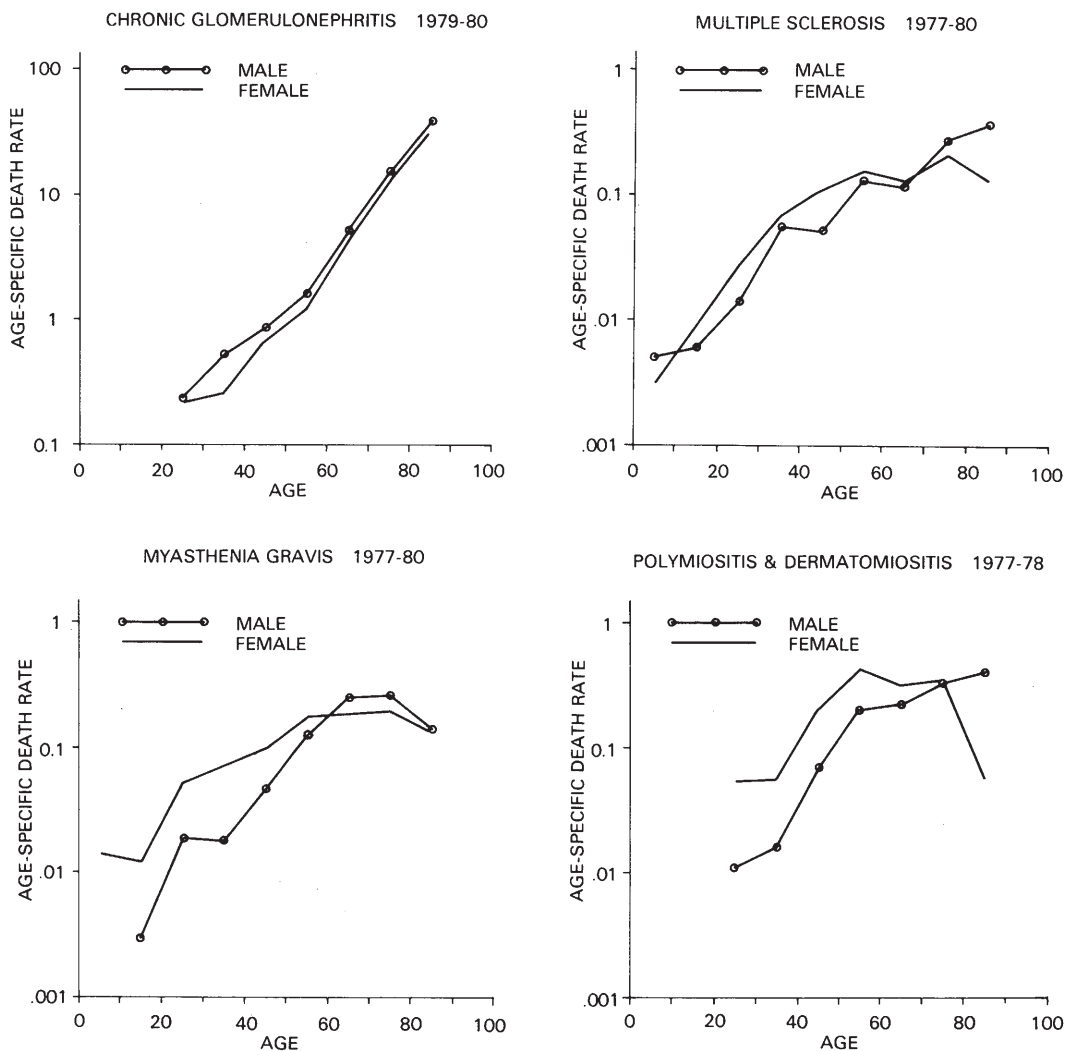


Fig. 2. 2 Distribution of Age Specific Death Rates per 100,000 population by Sex

Among seven intractable diseases in which females significantly predominated in Figures 2.2 and 2.3, chronic glomerulonephritis demonstrated the quite similar age curves to those in nephrotic syndrome and ulcerative colitis after 40 years of age. In the other intractable diseases of this group, age specific death rates were always higher in females than in males below 60 years of age in multiple sclerosis and myasthenia gravis and below 70 years of age in polymyositis and dermatomyositis, progressive systemic sclerosis and systemic lupus erythematosus. Magnitude of sex difference was seemingly unchanged by age between 20 or 30 and 49 or 69 years of age in four diseases of multiple sclerosis, thyrotoxicosis, progressive systemic sclerosis and systemic lupus erythematosus. In myasthenia gravis and polymyositis and dermatomyositis, sex difference in mortality seemed to decrease in magnitude with advancing ages up to the extreme ages or 79 years of age.

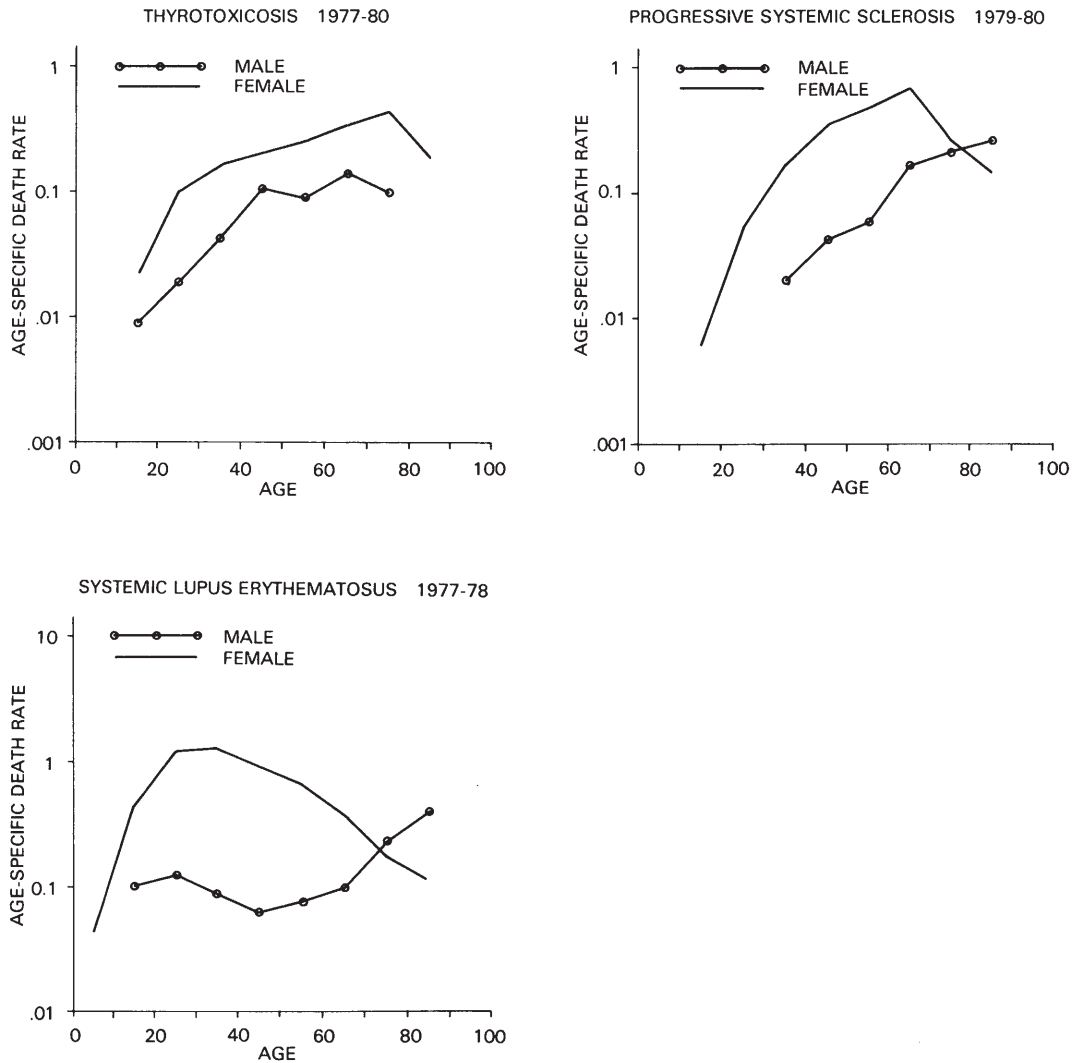


Fig. 2. 3 Distribution of Age Specific Death Rates per 100,000 population by Sex

Age curves of mortality in systemic lupus erythematosus were uniquely different: males seemingly demonstrated bimodal distribution by age; females showed the peaked mortality in 20-39 years of age with sharp increase in 0-19 years of age and with gradual decrease from 40 years of age. Of interest, in intractable diseases with sex ratio significantly below unity, was an apparent cross-over of two age curves of mortality approximately at 60-80 years of age, except in thyrotoxicosis and chronic glomerulonephritis.

DISCUSSION

In the present analysis sex difference was examined by a ratio of male deaths to female deaths. This simplest form of sex ratio is a fairly good measure of the difference in risk related to sex, when males and females equally share the population by sex. Since this is not always warranted, then the sex ratio calculated from age-adjusted rates between males and females are much more preferred. The statistical test of significance for this type of sex ratio, however, involves far more sophisticated statistical manipulations, which is now under deliberate investigation by the authors.

Male to female ratios of population were 0.969, 0.968 and 0.969 for 1977-1978, 1979-1980 and 1977-1980, respectively, with average populations of 56,111,500, 56,978,000 and 56,544,750 in males and of 57,894,500, 58,860,000 and 58,377,250 in females, correspondingly. Males were slightly less in number and populations were distributed with a minor shift to older ages in females. However, since this extent of sex differences in population and distribution is not material in a practical sense, then the sex ratio calculated from sex specific numbers of deaths is believed not seriously biased. In addition, this form of sex ratio is the simplest and the most easily calculable, and no intricate algebraic solution is advantageously involved even for obtaining the 95 percent confidence limits.

What interestingly emerged from the analysis were an appreciable predominance in intractable diseases for which autoimmune mechanisms seem responsible and either male or female predisposition to intractable diseases in which the vascular system is principally affected. These sex preponderances observed here are essentially identical to those reported by various research groups on each intractable disease.⁵⁻⁷⁾

Marked sex discrepancy in disease frequency is, in general, an important clue to the etiological insights into a given disease. Its etiological implications are, however, not as simple as deemed, since sex difference per se is a kind of end result of intricate interactions between intrinsic and extrinsic factors.

Nevertheless, when sex preponderance is quite substantial, likewise in thromboangitis obliterans and cardiomyopathy as well as systemic lupus erythematosus, progressive systemic sclerosis or thyrotoxicosis, some intrinsic and/or extrinsic factors which specifically affect either sex are to be etiologically incriminated. Conceivably, they are sex-determined biological differences in endocrine or immunometabolic responses as well as such environmental hazards as occupational exposures or life-style habits and customs, which include smoking and drinking habits and dietary practices. Differences in susceptibility intrinsically owing to sex, however, seem less readily documented.⁸⁾ When no sex differences are obvious, likewise in polyarteritis nodosa, nephrotic syndrome or ulcerative colitis, intrinsic and/or extrinsic factors that are commonly shared by sex may possibly be hypothesized.

In some intractable diseases, magnitude of sex difference in mortality appreciably varied by age. Changing magnitude of sex difference by age probably suggests the age-dependent contributions of intrinsic and/or extrinsic factors.

Accordingly, age-oriented as well as sex-oriented investigations which explicitly explore the attributes of age and sex differences are believed to be of extreme importance for each intractable disease. An attempt to investigate intractable diseases by group may also possibly be rewarding; diseases with marked sex difference as contrasted with those without, and diseases with definite male predominance as contrasted with those with substantial female preponderance.

APPENDIX

When the probability of death from a given disease is very small, the reasonable assumption is that the numbers of deaths from such a disease are distributed as Poisson variables.

Let n_m and n denote the numbers of male deaths and the total number of deaths in both sexes. By a well-known result, it follows that the proportion of male deaths ($p' = n_m/n$) is distributed as a binomial proportion with $p = R/(1 + R)$, where R is the true sex (male to female) ratio. Probability of the occurrence of n_m is given as

$$\binom{n}{n_m} p^{n_m} (1 - p)^{n - n_m}$$

Then, the 95 percent confidence limits for p is readily obtainable from the table of binomial distribution.

In case that n and n_m become large; this is generally true in epidemiological studies, male deaths follows a normal distribution with mean = np and variance = $np(1 - p)$. Then, the 95 percent confidence limits for p' ($= n_m/n$) are obtained, by a standard device, as

$$p - 1.96\sqrt{p(1 - p)/n} \leq p' \leq p + 1.96\sqrt{p(1 - p)/n}.$$

Substituting p by p' , the confidence limits are

$$p' - 1.96\sqrt{p'(1 - p')/n} \leq p \leq p' + 1.96\sqrt{p'(1 - p')/n}.$$

Since $R = p/(1 - p)$, the 95 percent confidence limits for R are then given as follows.

$$\frac{p' - 1.96\sqrt{p'(1 - p')/n}}{1 - (p' - 1.96\sqrt{p'(1 - p')/n})} \leq R \leq \frac{p' + 1.96\sqrt{p'(1 - p')/n}}{1 - (p' + 1.96\sqrt{p'(1 - p')/n})}$$

Thus, the significance of R could be statistically tested; R is regarded to be significantly different from unity, when above 95 percent confidence interval excludes 1.

REFERENCES

- 1) Health and Welfare Statistics Association: Kosei no Shihyo. Special edition, Kokumin Eisei no Doko. p. 190, 1981.
- 2) Research Council on Epidemiology of Intractable Diseases: Prefectural distribution of diseases specified by Ministry of Health and Welfare Japan, 1977-1980. Department of Preventive Medicine, Nagoya University School of Medicine, Nagoya. 1979-1982.
- 3) Asahi-shinbun-sha: Minryoku, 1977-1980, Tokyo. 1977-1980.
- 4) Ministry of Health and Welfare, Minister's Secretariat. Statistics and Information Department: Vital Statistics Japan, Vol. 2, 1977-1979. Vol. 3, 1980.
- 5) Epidemiology and intractable diseases in Japan. Special edition of Clinic All-Round, Vol. 26. Nagai-shoten, Tokyo, 1977.
- 6) Tokyo Medical Association: Gendai Tokutei-shikkan 40. Kanehara Printing Co. Ltd., Tokyo, 1977.
- 7) Ministry of Health and Welfare: Abstract of Researches on Specified Diseases, 1972-1978. 1980
- 8) Fox, J. P., Hall, C. E. and Elveback, L. R.: Epidemiology; Man and Disease. The Macmillan Co., New York, 1970.