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Cardiovascular disease, a major global burden: Epidemiology of stroke and ischemic heart disease in Japan

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Abstract: Japan ranks the highest globally, in terms of longevity. The average life expectancy was 81.4 years for men and 87.5 years for women in 2019. Such success in health is attributable to the substantial reduction in age-standardized mortality from cardiovascular diseases, especially stroke (136 per 10^5 in 1980 and 24 per 10^5 in 2015), when stroke mortality was the highest in the world between the 1960s and the 1990s. On the other hand, ischemic heart disease mortality was the lowest in the world between the 1960s and the 1980s and has continued to decline (40 per 10^5 in 1980 and 17 per 10^5 in 2015). Such a disease profile (larger burden of stroke compared to ischemic heart disease) was observed not only in Japan but also in some countries in central Asia and Africa, where small vessel disease (arteriolosclerosis) is assumed to be more common than large vessel disease (atherosclerosis). Between 1970 and 2015, a large decline in the population with high blood pressure levels was observed for both men and women. Meanwhile, there was a moderate decline in the smoking rate among men, and an increasing trend in serum cholesterol levels in both men and women. The sharp and extensive socioeconomic development between the 1960s and 1990s contributed to these health outcomes, while preventive measures and improved emergency medical care also contributed to the reduction of risk factors, disease incidence, case-fatality, and mortality. However, there is a threat of increasing incidence of ischemic heart disease in urban male employees and middle-aged male residents. Japan, with a super-aging society, needs to develop a new model for the prevention and control of cardiovascular disease and related health issues, with emphasis on efforts towards the early (primordial) prevention of cardiovascular disease as well as the attenuation of their progress towards chronic heart failure, chronic kidney disease, and vascular dementia.

***Keywords*:** cardiovascular disease, epidemiology, pathology, prevention, Japan

Introduction

Cardiovascular disease (mainly stroke and ischemic heart disease) is a major non-communicable disease, accounting for over two-thirds of total mortality worldwide (*1*). Cardiovascular disease is an emerging serious health issue in mid-to low-income countries as well as in high-income countries (*2*). However, the health burden of cardiovascular disease depends on the disease profile (the dominance of ischemic heart disease, stroke, or both diseases) as ischemic heart disease and stroke have differential demography (*3-5*), pathology (*6,7*), and clinical consequences (*8*).

There has been a steep decline in the mortality from stroke and ischemic heart disease in Japan, with the dominance of stroke compared to ischemic heart disease (2,9). The differences in etiologic factors and pathology attract scientific interest and also provide policymakers with a clue to construct preventive strategies for cardiovascular disease. Our experiences and evidence may be applied to other countries, especially in East Asia and Central Africa, where mortality from stroke is higher than that from coronary heart disease (*1,5*) which could be attributable to differential vascular pathology (*6,7*).

This article reviews the trends for stroke and ischemic heart disease with a look at the background lifestyles, and pathology in Japan compared to other countries.

Trends for mortality from stroke and ischemic heart disease

Japan had two- to three-fold higher mortality from stroke than the US, UK, and France in 1980, according to WHO statistics (Figure 1) (*2*). Between 1980 and 1990, stroke mortality declined more steeply in Japan than in western countries and continued to decline into 2015. On the other hand, mortality from ischemic heart disease in Japan was one-sixth, one-fifth, and half of that in the

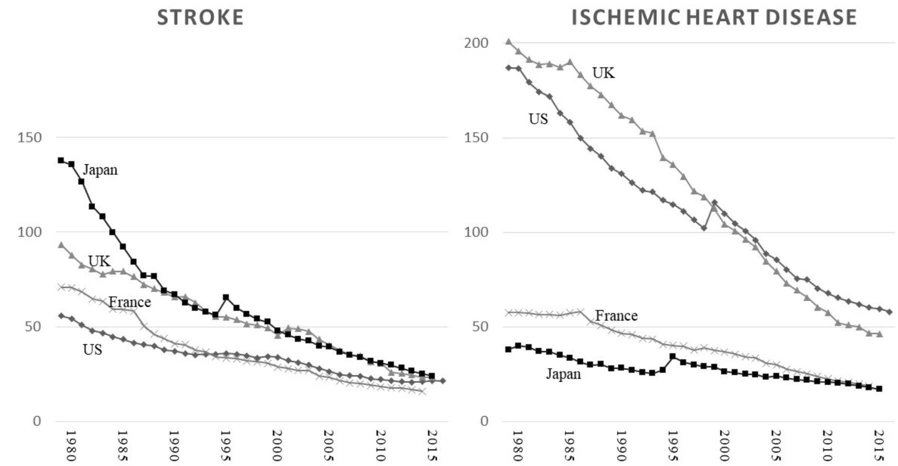

Figure 1. Age- and sex-adjusted mortality rate per 100,000, standardized to the standard WHO population, from stroke (A), ischemic heart disease (B), and stroke relative to ischemic heart disease. Source: Reference 2.

Table 1. Ratios of age- and sex-adjusted mortality rates from stroke and ischemic heart disease (IHD) per 100,000 in selected countries

Year	Japan Ratio	Stroke/IHD	US Ratio	Stroke/IHD	UK Ratio	Stroke/IHD	France Ratio	Stroke/IHD
1980	3.39	135.6/40.0	0.29	54.4/186.7	0.45	87.8/195.7	1.23	70.8/57.5
1985	2.75	92.3/33.6	0.27	43.4/158.1	0.42	79.4/190.1	1.03	59.2/57.3
1990	2.38	67.1/28.2	0.28	37.1/130.9	0.41	65.7/161.6	0.88	41.1/46.5
1995	1.91	65.3/34.1	0.31	35.9/114.7	0.41	55.2/135.7	0.84	33.5/40.1
2000	1.83	48.0/26.3	0.31	33.9/110.0	0.44	45.5/104.2	0.78	28.8/36.8
2005	1.64	39.4/24.0	0.31	26.3/85.5	0.51	40.4/79.3	0.78	23.4/29.9
2010	1.49	30.8/20.7	0.33	22.3/67.7	0.53	30.8/57.6	0.82	18.5/22.5
2015	1.40	24.0/17.1	0.36	21.6/59.5	0.51	23.5/46.3	0.85	16.0/18.8

US, UK, and France, respectively, in 1980, after which the mortality declined substantially. The magnitude of decline was larger in the US and the UK than in France and Japan. It is noteworthy that Japan, with the lowest mortality from coronary heart disease, showed a continuous decline in mortality, with the mortality in 2015 being half of what it was in 1995.

The ratio of stroke and ischemic heart disease mortality between 1980 and 2015, in Japan, was 3.39 in 1980 and 1.40 in 2015 (Table 1). The corresponding ratios were 0.29 and 0.36 in the US, 0.45 and 0.51 in the UK, and 1.23 and 0.85 in France. These findings indicate that the predominance of stroke in Japan has converted to being only moderately higher compared to ischemic heart disease, while ischemic heart disease has remained predominant in the US and UK. France showed trends between those of Asia and the US and the UK.

Kim *et al.* clearly illustrated that a higher mortality for stroke compared to ischemic heart disease, as seen in Japan, was also seen in other Asian countries, such as China, Mongolia, and Thailand; some European countries; and many central and southern African countries, according to the analysis of global variation in the relative burden of stroke and ischemic heart disease (*5*). The geographic differences in stroke and ischemic heart disease mortality suggest variation in pathology, risk factors, behaviors, and socio-economic factors.

Two types of vascular pathology and related factors

Such large differences in the profiles of cardiovascular diseases among countries can be explained by the lower proportion of large vessel pathology (atherosclerosis) and the higher proportion of small vessel pathology (arteriolosclerosis) in Japan than in the US and UK. The prevalence of arteriolosclerosis is probably higher, and that of atherosclerosis is lower, among urban residents than among rural residents of Japan because the incidence of ischemic heart disease was higher and that of stroke was lower in urban residents than in rural residents. For example, the incidence of ischemic heart disease in men aged 40-69 years in 1998 and 2003 was 127 and 65, respectively, and that of stroke was 118 and 231, respectively (*4*).

As shown in Figure 2, atherosclerosis is characterized by lipid accumulation and inflammatory cell proliferation, leading to the formation of 'plaque' and eventually, blood clot, which causes ischemic heart disease and ischemic (large vessel) stroke (*6,7*). High total cholesterol level (from a diet rich in saturated fat, such as meat), diabetes, smoking, and to a lesser extent, hypertension, accelerates this type of pathology. On the other hand, arteriolosclerosis is characterized by the death of smooth muscle cells, which constitute a major component of the vascular wall. This leads to the weakening of the vascular wall (constructed mainly by smooth muscle cells) and its subsequent rupture, or cell proliferation due to an excessive healing process, that causes intracerebral hemorrhage or ischemic (small vessel) stroke, namely lacunar stroke. Hypertension, and to a lesser extent, diabetes and smoking accelerate arteriolosclerosis. Low total or LDL-cholesterol levels (*10-12*), low intake of saturated fat (*13-15*), and low intake of protein (*13-16*) have been suggested to be linked to this type of pathology and intracerebral hemorrhage. A recent large observational and genetic study of the Chinese Kadoorie Biobank and a meta-analysis of randomized trials supported a causal relationship between lower LDL-cholesterol levels and a higher risk of intracerebral hemorrhage (*17*).

Strong trends for systolic blood pressure levels and stroke mortality

Figure 3 shows that sex- and age-specific mean value of systolic blood pressure, a strong risk factor for stroke, declined substantially between 1970 and 2019 among national representative samples of men and women aged ≥ 30 years (*18*). For both men and women, systolic blood pressure levels have declined substantially in all age categories with a larger decline among older ages than younger ages, and with a larger decline between 1970 and 1990 than thereafter. Meanwhile, age-adjusted stroke mortality peaked in 1965 and declined materially from 1965 to 1990 for both men and women. After 1990, stroke mortality continued to decline although the rate of decline became smaller (Figure 4) (*19*).

Figure 5 illustrates trends for cardiovascular risk

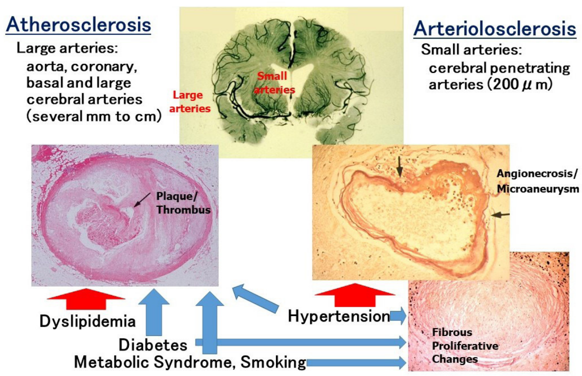

Figure 2. Two types of vascular pathology and related factors, atherosclerosis and arteriolosclerosis. Source: References 7.

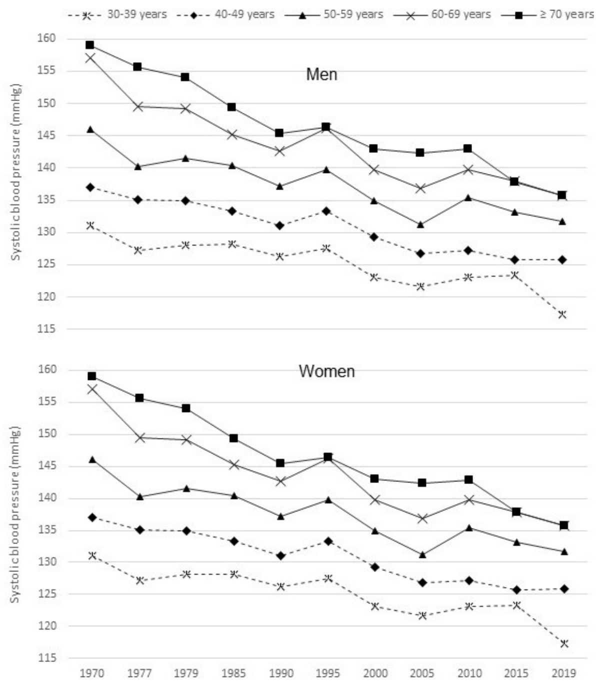

Figure 3. Sex- and age-specific trends for systolic blood pressure levels between 1970 and 2019. Source: National Health and Nutrition Survey, Reference 18.

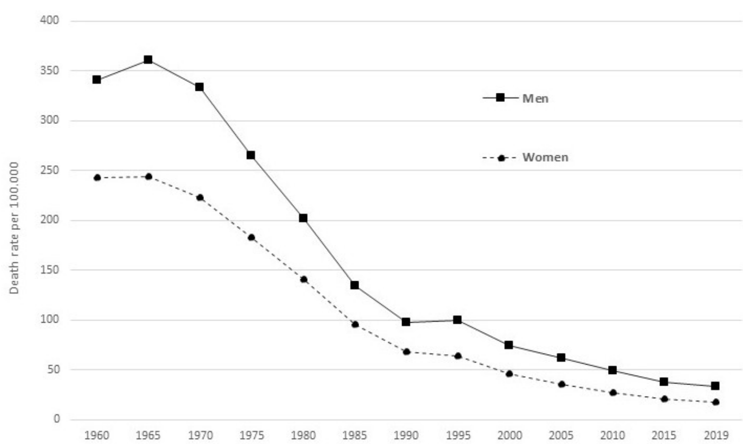

Figure 4. Sex-specific trends for age-adjusted mortality rates per 10,000, standardized to the 1960 Japan national standard population, for stroke between 1960 and 2019. Source: Reference 19.

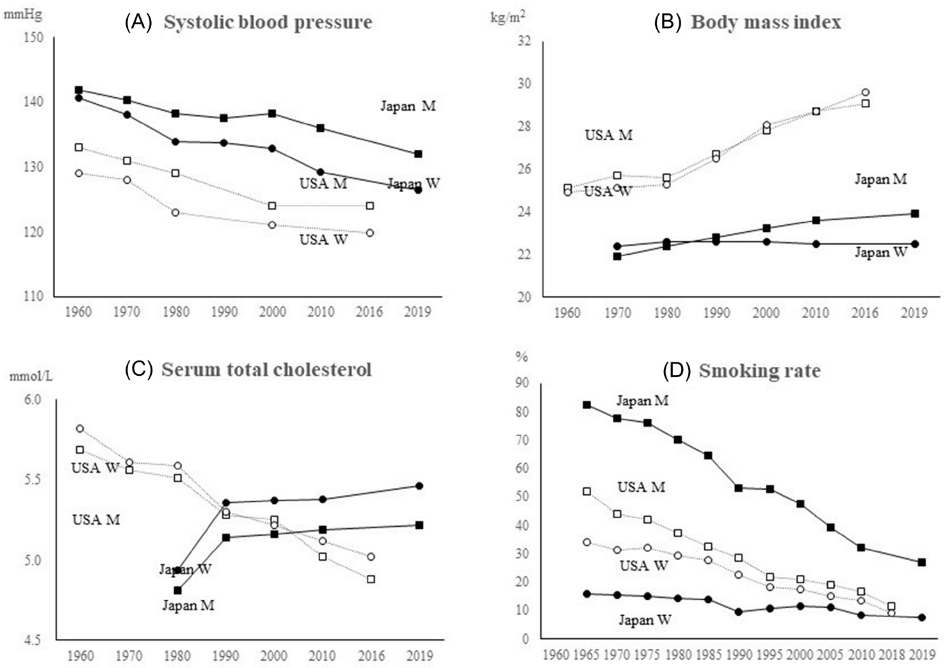

Figure 5. Sex-specific trends for cardiovascular risk factors such as mean levels of systolic blood pressure (A), body mass index (B), serum total cholesterol (C), and smoking rate (D) in national samples of Japan and the US between 1960 and 2019.

factors such as mean values of systolic blood pressure, body mass index (BMI), serum total cholesterol and smoking rate in Japan and the US between 1960 and 2019. Although mean systolic blood pressure levels were higher in Japanese adult men and women than their US counterparts, levels declined substantially in all groups (*18,20,21*). Mean BMI was much lower in Japanese than in Americans throughout the years while mean BMI in Americans has increased continuously since 1980 (*18,22,23*). Mean blood cholesterol in Japanese men and women increased from 1980 to 1990 to match that of their American counterparts, after which they stabilized while American levels continued to decline. Smoking rate was much higher in Japanese men and much lower in Japanese women compared with Americans (*18,24,25*). Although the rate declined substantially it still remains relatively high in Japanese men (*18,26*).

These strong trends for blood pressure and stroke mortality have been attributed to nutritional improvements, such as reduced salt intake, balanced intake of fresh vegetables, fruits, fish, and meat, and the reduction of hard labor due to mechanization (*27*). Increased blood total cholesterol in the Japanese may reflect an increased intake of saturated fat from meat and dairy products (*18*). These lifestyle changes were enhanced by rapid and large economic development between the 1960s and 1990s (*7,8*). The substantial decline in stroke mortality has also been attributed to the improvement in emergency medical care since the late 1970s. A community-based registry reported that the case-fatality rate within one month declined substantially for stroke: 22.0% in 1977-1981, 19.9% in 1982-1986, and 16.5% in 1987-1991 (*28*).

Effects of a community-based stroke prevention program

The question is whether such a large decline in blood pressure and stroke mortality is caused by economic development. The answer is partly yes.

Our research team launched a stroke prevention program in several communities in the early 1960s, after the initiation of the 1961 universal health coverage (*29*). The program consisted of systematic blood pressure screening for the detection of hypertension through annual health check-ups for individuals aged ≥ 30 years, referral of severe hypertensive and other high-risk individuals to local physicians, health instructions for lifestyle modification by physicians, public health nurses, and nutritionists on an individual and group basis, adjunct activities by health volunteers, and community-wide media campaigns for health education (*29*). As shown in Figure 6, the program achieved a larger decline in systolic blood pressure levels by 3 to 4 mmHg, and a larger reduction in stroke incidence by 21% (*32,33*) with a cost-saving effect on public health services (including salaries of health professionals and clerical workers and costs of screening and related health activities) and medical care (treatment for hypertensive and stroke patients) (*31*), compared to a reference community.

A 3.5-year community-based intervention trial in seven cities in China in 1987 demonstrated a program requesting people with hypertension and a history of

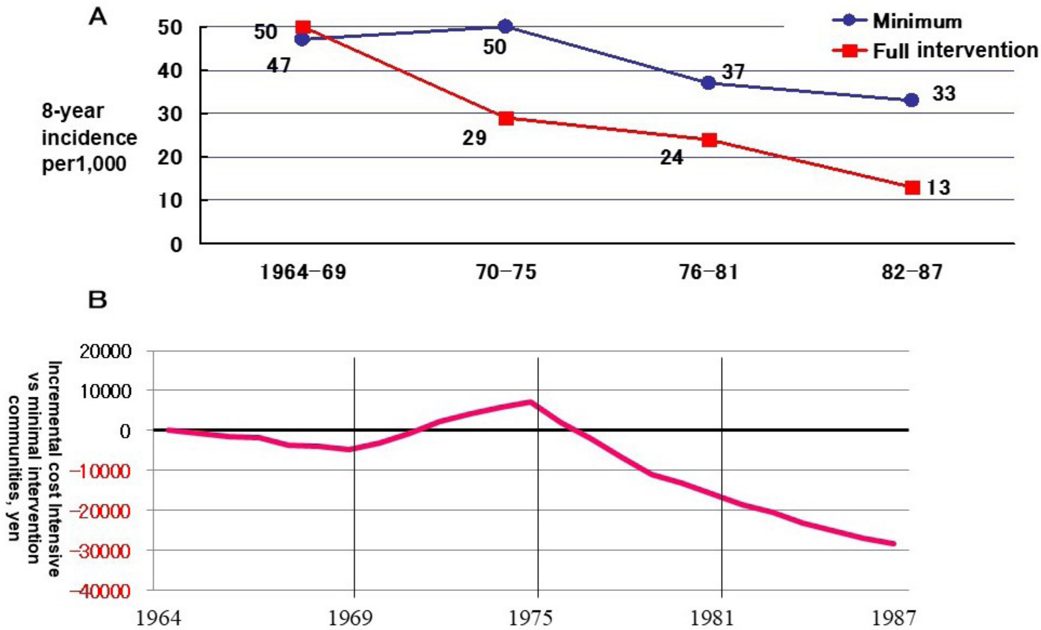

Figure 6. Sex- and age-adjusted 8-year incidence per 1,000 of stroke (A) and incremental cost (yen per capita) (B) in the full intervention versus minimum intervention communities from 1964 to 1987. Source: References 21, 24.

diabetes or heart disease to visit the clinic regularly for treatment (drug treatment and lifestyle intervention including weight reduction, increased physical activity, and modification of dietary sodium and alcohol intake) along with community-based health education. The program was feasible and effective in reducing the incidence of stroke by 31% more than the control cohort (*32*).

The future threat of increasing incidence of ischemic heart disease

What is the future health issue regarding cardiovascular disease in Japan, where mortality from stroke and ischemic heart disease has been declining since the 1960s? The answer is a threat of an increasing incidence of ischemic heart disease in some populations. Trends for ischemic heart disease mortality varied by sex, age, and regions; the decrease in mortality was lesser among men residing in the Tokyo and Osaka metropolitan cities than among those in the rest of Japan (*33*). There was no substantial change in mortality among men aged 30-49 years (around 10 per 100,000), whereas those in the rest of Japan showed a steady decline between 1969-1970 and 1989-1990. This was probably due to a substantial decline in blood pressure levels for both men and women and a moderate reduction in the smoking rate for men, albeit with increased cholesterol levels. The improvement of emergency medical care also contributed to the decline in coronary heart disease mortality, and a prefecture-based registry showed that the case-fatality rate within one month for acute myocardial infarction was 17.0%, 13.1%, 9.1%, and 7.3% in 1980-1984, 1985-1989, 1990-1994, and 1995-1999, respectively (*34*).

Age-adjusted incidence of ischemic heart disease increased from 0.4 per 1,000 person-years between 1963 and 1970 to 1.5 per 1,000 person-years between 1979 and 1986, and plateaued until 1987-1994 among male employees aged 40-59 in Osaka (*35*). A similar trend was observed for Osaka male residents aged 40 to 69 years, with an increased incidence per 100,000 person-years from 56 in 1980-1987 to 127 in 1996-2003 (*4*). In contrast, the incidence of ischemic heart disease remained low and did not change among female residents in Osaka (from 1,336 to 23 per 100,000 person-years) (*35*). The increasing incidence of ischemic heart disease in middle-aged men is probably due to increased blood cholesterol levels, physical inactivity, and reduced intake of fish (*8*).

Conclusions

In the face of a super-aging society (*36*), Japan needs to develop a new model for the prevention and control of cardiovascular diseases and related health issues. We need to make efforts in public health services and medical care towards the early (primordial) prevention of cardiovascular disease, as well as the attenuation of their progress towards chronic heart failure, chronic kidney disease, and vascular dementia. To enhance early prevention, data from pre-birth to old age, segregated among different administrative sections are urgently required. Nevertheless, our success in cardiovascular health so far provides valuable clues for other countries with a rapidly aging population, especially in Asia and the mid-East (*37*).

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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