



Cardiovascular Epidemiology

Continuous decline in mortality from coronary heart disease in Japan despite a continuous and marked rise in total cholesterol: Japanese experience after the Seven Countries Study

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Abstract

Background: The Seven Countries Study in the 1960s showed very low mortality from coronary heart disease (CHD) in Japan, which was attributed to very low levels of total cholesterol. Studies of migrant Japanese to the USA in the 1970s documented increase in CHD rates, thus CHD mortality in Japan was expected to increase as their lifestyle became Westernized, yet CHD mortality has continued to decline since 1970. This study describes trends in CHD mortality and its risk factors since 1980 in Japan, contrasting those in other selected developed countries.

Methods: We selected Australia, Canada, France, Japan, Spain, Sweden, the UK and the USA. CHD mortality between 1980 and 2007 was obtained from WHO Statistical Information System. National data on traditional risk factors during the same period were obtained from literature and national surveys.

Results: Age-adjusted CHD mortality continuously declined between 1980 and 2007 in all these countries. The decline was accompanied by a constant fall in total cholesterol except Japan where total cholesterol continuously rose. In the birth cohort of individuals currently aged 50–69 years, levels of total cholesterol have been higher in Japan than in the USA, yet CHD mortality in Japan remained the lowest: >67% lower in men and >75% lower in women compared with the USA. The direction and magnitude of changes in other risk factors were generally similar between Japan and the other countries.

Conclusions: Decline in CHD mortality despite a continuous rise in total cholesterol is unique. The observation may suggest some protective factors unique to Japanese.

Key words: Coronary heart disease, international trend, risk factors, total cholesterol, Japan, Western countries

Key Messages

- This paper described trends in mortality from coronary heart disease and total cholesterol as well as other risk factors since 1980, highlighting the trends in Japan and contrasting those in other selected developed countries: Australia, Canada, France, Spain, Sweden, the UK and the USA.
- Age-adjusted mortality from coronary heart disease continuously declined between 1980 and 2007 in all these countries.
- The decline in age-adjusted mortality from coronary heart disease was accompanied by a constant fall in total cholesterol except for Japan where total cholesterol continuously rose.
- The direction and magnitude of changes in other risk factors were generally similar between Japan and the other countries.
- The observations may suggest some protective factors unique to Japanese in Japan.

Introduction

The Seven Countries Study in the 1960s reported a 5-fold difference in mortality from coronary heart disease (CHD): the lowest in Japan and Southern Europe and the highest in Northern Europe and the USA.¹ The difference in CHD mortality was partly attributed to a marked difference in blood levels of total cholesterol: 4.25 mmol/l in Japan vs. 6.20 mmol/l in the USA. The low levels of total cholesterol in Japan were due to their low dietary intake of saturated fat and cholesterol. Based on this and other numerous studies, blood levels of total and low-density-lipoprotein (LDL) cholesterol were established as one major risk factor for CHD. Both individual-based diet and drug trials document that lowering levels of total or LDL cholesterol reduces the risk of CHD.^{2,3}

Studies of migrant Japanese to the USA in the 1970s reported a dramatic increase in CHD rates within one generation of migration.⁴ It was thus expected that exposures to more a Westernized lifestyle among native Japanese after World War II (WWII), for example increase in dietary intake of saturated fat, would cause sizeable rise in blood total cholesterol, leading to a considerable increase in CHD rates in Japan. Between 1960 and 1990, dietary intake of fat and cholesterol in Japan more than doubled.⁵ The current levels of blood total cholesterol in Japan, especially among individuals born after WWII, are comparable to those in other developed countries,⁶ very

different from the 2-mmol/l difference in total cholesterol at the time of the Seven Countries Study. Moreover, age-adjusted mortality from other diseases related to Westernized lifestyle, such as colon, breast and prostate cancers, more than doubled during this period.⁷ Very surprisingly, age-adjusted CHD mortality in Japan started to decline in 1970 as in Western countries, and has remained one of the lowest in developed countries: >67% lower in men and >75% lower in women compared with the USA,⁸ accounting partly for the greatest longevity in the world among Japanese.⁹ This study describes trends in CHD mortality and its risk factors since 1980, highlighting the trends in Japan and contrasting those in other selected developed countries.

Methods

Data on CHD mortality were obtained from the World Health Organization (WHO) Statistical Information System [www.who.int/whosis]. A new WHO standard¹⁰ was used to calculate age-adjusted mortality for men and women aged 35–74 years. To define CHD, we used codes I20–25 in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and codes 410–414 in ICD-9. To examine the trends, we used 4-year average CHD mortality between 1980 and 2007, that is 1980–83 to 2004–07. To depict the

international trend in CHD mortality from 1980 to 2007, we chose Australia, Canada, France, Japan, Spain, Sweden, the UK and the USA.

Data on age-adjusted mean levels of total cholesterol, systolic blood pressure, rates of current smokers and body mass index (BMI), as well as age-adjusted prevalence of diabetes, were obtained from recent Global Burden of Disease publications^{6,11–14} which describe their trends between 1980 and 2008 in each of the above and other countries. These data are based on extensive search of published and unpublished national health surveys and epidemiological studies, and thus are considered to be the best available data to illustrate and compare the trends across countries in this period.

To compare age- and sex-specific trends in total cholesterol between Japan and the USA, data were obtained from national surveys in each country.^{15–18}

Results

In 1980–83, Japan had the lowest age-adjusted mortality from CHD; a 6- to 7-fold difference in age-adjusted CHD mortality existed among these countries: 62.4/100 000 in Japan vs 367.0/100 000 in the USA for men and 27.3/100 000 in Japan vs 134.7/100 000 in the USA for women (Table 1). Between 1980–83 and 2004–07, age-adjusted CHD mortality in Japan declined by 26.7% in men and 50.7% in women. The percentage of decline in women in Japan was comparable to that in other countries whereas that in men was less than a half. There remained a 3- to 5-fold difference, that is 45.8/100 000 in Japan vs 150.7/100 000 in the USA for men and 13.5/100 000 in Japan vs 60.6/100 000 in the USA for women (Table 1).

Between 1980 and 2008, age-adjusted mean levels of total cholesterol steadily rose in Japan in striking contrast to constant fall in total cholesterol in all other countries (Figure 1; Supplementary Table 1, available as Supplementary data at *IJE* online). The larger part of the rise in cholesterol in Japan occurred between 1980 and 1990.

Levels of total cholesterol in individuals aged 50–69 years in 2008 were higher in Japan than in the USA for both sexes (Figure 2; Supplementary Table 2, available as Supplementary data at *IJE* online). In this birth cohort, levels of total cholesterol 20 years ago, that is among individuals aged 30–49 years in 1990, were similar between Japan and the USA for both sexes.

Age-adjusted mean levels of systolic blood pressure continuously fell between 1980 and 2008 both in Japan and in the other countries (Table 2). The magnitude of the fall in Japan during this period was comparable to that in the other countries.

Similarly, age-adjusted prevalence of smoking fell between 1980 and 2012 both in Japan and in the other developed countries (Table 3). In men, rates of current smokers in Japan remained highest among these countries during this period: 20–30% higher compared with the USA.

In most of the countries, including Japan, age-adjusted prevalence of diabetes rose from 1980 to 2008 (Table 4). During this period, the prevalence in Japan rose by 3.4% in men and by 1.4% in women. The age-adjusted prevalence of diabetes in Japan in 2008 was similar to that in France and was lower compared with the USA and Canada.

Age-adjusted levels of BMI rose between 1980 and 2008 in all the countries for both sexes (Table 5). Levels of BMI in Japan rose during this period by 1.4 kg/m² in men and 0.6 kg/m² in women; the mean BMI and prevalence of obesity remained much lower in Japan compared with those in the other countries.

Discussion

Our study illustrated opposite directions of trends in population-levels of total cholesterol between Japan and Western countries, despite decline in age-adjusted CHD mortality between 1980 and 2008 in all these countries. Our study also showed that the magnitude of changes in other major risk factors during this period was generally similar across these countries.

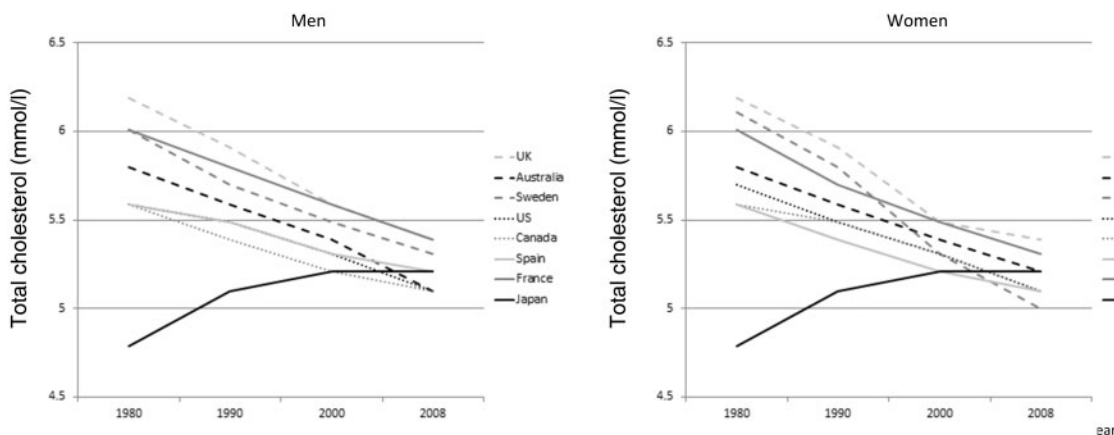
The declining trend in CHD mortality in these countries that started around 1970 is attributable to two factors: a better population profile of risk factors which leads to reduced CHD incidence and improved treatment for CHD. The decline in CHD mortality between the 1980s and 2000s in Canada,¹⁹ Italy,²⁰ Sweden,²¹ the UK²² and the USA²³ is attributable to reductions in major risk factors by 40–60% and to improved treatment by about 40%. The fall in population-levels of total cholesterol is a major contributor to the decline in CHD mortality. CHD mortality in Japan started to decline in 1970: the fact that population-levels of total cholesterol steadily and markedly rose in Japan during the past five decades is counterintuitive.

Substantial increase in CHD mortality occurred in the first half of the 20th century in Western countries and is now taking place in developing countries.²⁴ Although data are limited on specific causes for the increase, a recent study in Beijing, China, conducted between 1984 and 1999, shows that the rise in population-levels of total cholesterol accounts for 77% of the increase in CHD mortality.²⁵ During this period, CHD mortality in China increased by 50% in men and 27% in women; population-levels of total cholesterol rose by 1 mmol/l. The magnitude

Table 1. Trend in age-adjusted mortality from coronary heart disease (/100 000) between 1980–83 and 2004–08 in men (A) and women (B)

(A) Men								
	1980–83	1984–87	1988–91	1992–95	1996–99	2000–03	2004–07	% change ^a
UK	460.3	430.5	364.7	307.4	245.3	189.7	143.7	–68.8
Australia	389.3	326.9	260.1	202.7	160.3	119.5	89.5	–77.0
Sweden	381.4	336.9	270.0	222.7	174.4	134.8	111.4	–70.8
USA	367.0	303.3	253.1	220.8	197.5	183.7	150.7	–58.9
Canada	358.2	301.7	242.2	195.9	164.9	134.8	114.6	–68.0
Spain	137.4	134.7	122.6	116.5	112.2	96.1	80.9	–41.4
France	132.5	125.7	100.0	87.9	78.8	68.8	55.5	–58.1
Japan	62.4	52.0	44.4	45.0	51.8	48.8	45.8	–26.7
(B) Women								
	1980–83	1984–87	1988–91	1992–95	1996–99	2000–03	2004–07	% change ^a
UK	154.4	150.9	132.5	111.5	88.0	65.6	46.6	–69.8
Australia	140.1	121.7	96.4	74.0	55.6	40.3	26.5	–81.1
Sweden	110.2	94.6	80.1	67.9	55.1	45.9	35.0	–68.3
USA	134.7	117.1	99.1	88.0	80.9	75.5	60.6	–55.0
Canada	120.7	101.5	82.1	67.0	55.8	44.6	37.5	–68.9
Spain	39.2	36.6	33.7	31.5	28.9	24.3	19.9	–49.3
France	36.9	34.1	24.9	21.6	18.5	15.5	12.0	–67.7
Japan	27.3	21.6	17.4	16.6	17.6	15.2	13.5	–50.7

^a% change was calculated as the difference between CHD mortality in 1980–83 and 2004–07 divided by CHD mortality in 1980–83. We first calculated age-adjusted CHD mortality in each year from 1980 through 2007. Then we averaged the mortality in 4-year periods, e.g. 1980–83, 1984–87 and so forth. The WHO Statistical Information System did not provide data in 2005 in Australia nor in 2006 and 2007 in Canada; thus we averaged the data in 2004, 2006 and 2007 for Australia and 2004 and 2005 for Canada for CHD mortality in 2004–07 in each country.

**Figure 1.** Trends in age-adjusted levels of total cholesterol in Japan and selected developed countries between 1980 and 2008 by sex (mmol/l). Data are from reference 6. Actual numerical data are in [Supplementary Table 1](#).

of rise in total cholesterol is similar to that the Japanese experienced between the 1960s and 1990s.

The low CHD mortality in Japan is not due to a misclassification of cause of death or a competing risk. Incidence of myocardial infarction in multiple registries in Japan, using the WHO MONICA criteria, was much lower than in registries in all industrialized countries or even China, according to the WHO MONICA study.²⁶ Though

stroke mortality in Japan was highest in developed countries in the 1960s, the mortality dropped by almost 80% between 1965 through 1990.²⁶ Current stroke mortality is similar to that in other developed countries.⁹ Moreover, age-adjusted total mortality in Japan is lower by 20% in men and 40% in women compared with the USA.⁸

The low CHD mortality in Japan is unlikely to be due to genetics. Studies of Japanese migrants to the USA

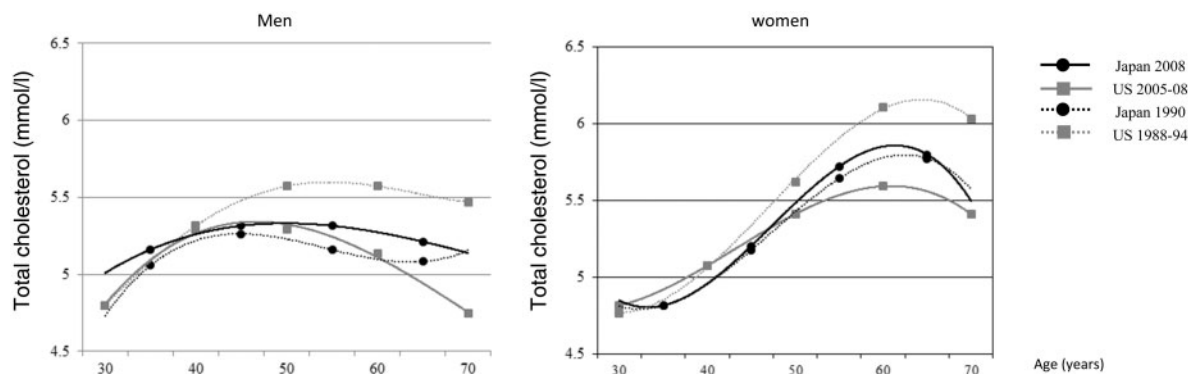


Figure 2. Trends in total cholesterol (mmol/l) in Japan and the USA between 1990 and 2008 by sex from national surveys. The data in Japan of 1990 are from the National Cardiovascular Survey (reference 15) which was recently integrated into the National Health and Nutrition Survey, and the data of 2008 were from this survey. These surveys in Japan are cross-sectional on a nationally representative sample of the non-institutionalized population of Japan (reference 16). Moreover, in these surveys total cholesterol was measured under the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention in the USA (references 15 and 17); thus data are directly compared with those in the USA. The data in the USA of 1988–94 and 2005–08 were from the National Health and Nutrition Examination Surveys (reference 18). Numerical data were shown in Supplementary Table 2.

Table 2. Trend in age-adjusted systolic blood pressure (mmHg) between 1980 and 2008 in selected countries by sex

	Men					Women				
	1980	1990	2000	2008	Diff ^a	1980	1990	2000	2008	Diff ^a
UK	136.5	136.5	134.8	131.2	-5.3	131.0	131.6	128.9	124.1	-6.9
	131.2–141.8	133.8–139.2	132.4–137.1	127.5–134.9		125.0–136.6	128.8–134.5	126.5–131.3	120.0–128.1	
Australia	134.3	132.8	130.6	127.2	-7.1	128.8	125.7	121.5	117.4	-9.4
	128.2–140.4	129.9–135.6	127.9–133.3	121.3–132.7		122.7–135.0	122.9–128.7	118.6–124.3	11.6–122.8	
Sweden	138.8	134.2	132.9	131.7	-7.1	132.9	129.3	125.8	122.9	-10.0
	133.7–144.1	131.3–137.1	129.9–136.0	126.9–137.0		126.6–139.0	126.1–132.3	122.9–128.7	117.7–128.5	
USA	131.2	127.4	124.3	123.3	-7.9	125.4	122.1	120.1	118.5	-6.9
	127.2–135.3	124.5–130.2	121.9–126.6	119.8–126.7		121.1–129.6	119.1–124.9	117.7–122.4	115.0–122.0	
Canada	131.0	129.8	126.8	123.6	-7.4	124.9	123.5	121.3	118.1	-6.8
	126.2–135.9	126.2–133.5	122.5–131.5	118.0–129.0		120.2–129.4	120.0–127.1	116.5–125.8	11.3–124.4	
Spain	136.6	131.6	130.3	130.4	-6.2	133.5	127.9	124.1	122.0	-11.5
	130.6–142.9	128.9–134.3	127.7–132.9	125.8–134.8		127.6–140.1	125.0–130.6	121.4–126.8	117.3–126.9	
France	138.8	134.8	132.9	131.0	-7.8	132.1	127.9	123.8	120.0	-12.1
	132.1–145.7	131.2–138.4	129.5–136.5	126.6–135.7		124.9–139.7	124.0–131.8	120.1–127.4	115.4–124.6	
Japan	136.8	132.7	131.1	130.5	-6.3	131.2	127.7	124.6	122.0	-9.2
	133.5–140.1	130.9–134.4	129.3–132.9	126.9–133.9		128.1–134.3	126.0–129.3	122.9–126.3	118.6–125.2	

Data are expressed as mean and uncertainty interval (reference 11).

^aThe difference in age-adjusted systolic blood pressure between 1980 and 2008.

documented a dramatic increase in CHD rates.⁴ Additionally, Japanese Americans had higher levels of atherosclerosis, a major underlying cause of CHD, than White Americans. We compared well-established biomarkers of atherosclerosis, coronary artery calcification and carotid intima-media thickness, in population-based samples of middle-aged native Japanese, White Americans and third-generation Japanese Americans without ethnic admixture.²⁷ Despite a similar profile of risk factors, Japanese Americans had higher levels of atherosclerosis compared with not only native Japanese but also White Americans.

CHD mortality in Japan increased between 1992–95 and 1996–99 in both sexes. The increase is largely due to changes in coding practice for death certification. Before the 10th revision of the ICD was introduced in 1995, the Ministry of Health in Japan issued in 1994 guidance not to put heart failure as primary cause of death in terminal stage or sudden death. As a result, mortality from heart failure decreased by 60–70% and mortality from CHD increased by 20–30% between 1993 and 1995.^{28,29} Taking the change into consideration, the decline in age-adjusted CHD mortality in women was rather similar before and after 1995, whereas that in men appeared to be attenuated

Table 3. Trend in age-adjusted rates of current smokers (%) between 1980 and 2012 in selected countries by sex

	Men					Women				
	1980	1996	2006	2012	Diff ^a	1980	1996	2006	2012	Diff ^a
UK	38.8	30.4	25.6	23.0	-15.8	38.0	29.5	23.6	20.1	-17.9
	36.7-41.0	29.5-31.4	24.7-26.4	20.9-25.2		35.6-40.5	28.3-30.7	22.6-24.6	19.0-21.2	
Australia	34.3	25.6	20.8	18.3	-16.0	27.3	22.6	17.2	15.4	-11.9
	31.8-37.2	24.3-26.9	19.3-22.2	16.4-20.1		24.3-30.6	21.1-24.1	15.6-18.9	13.5-17.5	
Sweden	30.3	19.7	11.1	12.3	-18.0	28.7	24.8	15.1	14.8	-13.9
	28.5-32.0	18.6-20.9	10.5-11.8	11.0-13.8		26.6-30.9	23.2-26.4	14.1-16.2	13.0-16.8	
USA	33.2	23.1	19.7	17.2	-16.0	28.3	20.1	16.4	14.3	-14.0
	29.9-36.7	22.2-24.2	18.9-20.5	16.3-18.2		24.2-32.5	19.0-21.2	15.6-17.3	13.3-15.5	
Canada	42.3	27.4	18.1	16.7	-25.6	34.1	24.6	14.3	12.8	-21.3
	39.0-45.5	26.0-29.0	17.0-19.2	15.4-18.3		30.4-37.8	22.9-26.2	13.3-15.4	11.5-14.1	
Spain	44.4	41.0	31.7	29.5	-14.9	28.3	27.7	25.7	23.2	-5.1
	39.4-49.6	38.9-43.0	29.9-33.3	26.9-32.2		22.8-34.1	25.7-29.7	23.7-27.6	20.3-26.4	
France	41.5	37.9	33.3	34.4	-7.1	18.8	30.1	27.0	27.7	+8.9
	38.6-44.7	35.8-39.9	31.2-35.6	30.8-38.0		16.4-21.5	28.0-32.3	24.6-29.4	24.0-31.6	
Japan	60.8	51.9	40.9	35.3	-25.5	13.0	12.7	13.1	11.2	-1.8
	57.9-64.0	49.6-55.1	38.3-43.8	32.4-38.5		11.5-14.7	11.7-14.0	12.0-14.3	9.6-13.0	

Data are expressed as mean and uncertainty interval (reference 14).

^aThe difference in age-adjusted prevalence of diabetes between 1980 and 2012.

Table 4. Trend in age-adjusted prevalence of diabetes (%) between 1980 and 2008 in selected countries by sex

	Men					Women				
	1980	1990	2000	2008	Diff ^a	1980	1990	2000	2008	Diff ^a
UK	8.1	7.4	7.4	7.8	-0.3	5.7	5.9	5.7	5.7	0.0
	2.0-19.2	4.5-11.2	4.7-10.6	3.8-13.4		1.3-14.4	3.5-8.8	3.7-8.3	2.7-10.1	
Australia	5.9	6.7	8.3	9.6	+3.7	4.6	4.9	6.0	6.7	+2.1
	2.5-11.0	3.6-10.7	5.4-12.2	4.4-16.9		2.0-8.6	2.6-8.1	3.8-8.8	2.9-12.2	
Sweden	6.9	6.0	6.6	8.1	+1.2	7.5	6.9	6.0	6.0	-1.5
	1.7-16.6	3.6-9.1	3.6-10.6	2.5-17.0		0.6-12.5	4.1-10.4	3.1-9.7	1.6-13.6	
USA	6.1	8.1	10.3	12.6	+6.5	5.1	6.4	7.6	9.1	+2.8
	2.9-10.7	2.7-16.8	7.2-14.1	8.1-18.1		2.4-8.9	3.9-9.8	5.3-10.4	5.7-13.3	
Canada	7.6	8.1	9.4	10.9	+3.3	5.5	6.0	7.0	8.3	+2.8
	1.1-21.2	2.7-16.8	3.4-19.1	2.5-26.3		0.7-16.7	1.8-13.7	2.1-15.6	1.6-20.9	
Spain	5.2	5.5	7.8	11.0	+5.2	4.4	4.5	6.2	8.8	+4.4
	1.0-14.0	3.0-8.8	5.3-11.0	5.9-18.5		0.6-12.5	2.4-7.3	4.1-8.8	4.5-15.2	
France	7.1	7.0	7.1	7.2	+0.1	4.9	5.1	4.8	4.3	-0.6
	1.2-19.2	3.3-12.3	4.3-10.8	3.3-12.6		0.7-14.6	2.3-9.1	2.7-7.6	1.9-7.8	
Japan	3.8	4.9	6.3	7.2	+3.4	3.3	4.2	4.9	4.7	+1.4
	1.0-8.7	3.5-6.5	4.6-8.2	4.5-10.4		1.0-7.2	3.0-5.6	3.6-6.5	2.9-7.0	

Data are expressed as mean and uncertainty interval (reference 13).

^aThe difference in age-adjusted prevalence of diabetes between 1980 and 2008.

after 1995 (Supplementary Figure 1, available as Supplementary data at *IJE* online). Therefore it is of critical importance to carefully monitor trends in CHD mortality in men in Japan.

Our observation: in Japan the decline in CHD mortality, despite a continuous and marked rise in total cholesterol, is in accordance with a recent report from the Hisayama study.³⁰ The study consists of a series of

population-based cohorts of several thousand subjects in each decade since the 1960s in Hisayama, Japan.³⁰ The study revealed no increase in age-adjusted CHD incidence or mortality between the cohorts in the 1960s through 2000s despite a substantial rise in age-adjusted total cholesterol (1.2 mmol/l).

Is total cholesterol not a risk factor for CHD in the Japanese? Prospective cohort studies in Japan have

Table 5. Trend in age-adjusted levels of body mass index (kg/m²) between 1980 and 2008 in selected countries by sex

	Men					Women				
	1980	1990	2000	2008	Diff ^a	1980	1990	2000	2008	Diff ^a
UK	24.7 23.9–25.6	25.6 25.2–26.0	26.6 26.4–26.9	27.4 26.9–27.9	+2.7	24.2 23.2–25.2	25.2 24.8–25.7	26.2 25.9–26.6	26.9 26.3–27.6	+2.7
Australia	24.9 24.3–25.6	25.8 25.4–26.2	26.7 26.4–27.1	27.6 27.0–28.1	+2.7	23.6 22.8–24.4	24.9 24.4–25.4	26.0 25.6–26.5	26.9 26.2–27.6	+3.3
Sweden	24.7 23.7–25.8	25.2 24.8–25.6	25.8 25.4–26.1	26.4 25.6–27.2	+1.7	24.4 23.0–25.7	24.6 24.0–25.2	24.9 24.4–25.5	25.1 24.1–26.2	+0.7
USA	25.5 25.0–26.0	26.6 26.2–27.0	27.7 27.4–28.0	28.5 28.0–28.9	+3.0	25.0 24.3–25.8	26.3 25.8–26.8	27.5 27.1–27.9	28.3 27.7–28.9	+3.3
Canada	25.2 24.6–25.8	26.1 25.7–26.5	27.0 26.5–27.4	27.5 27.0–28.0	+2.3	24.1 23.3–24.9	25.1 24.6–25.6	26.1 25.6–26.7	26.7 26.0–27.4	+2.6
Spain	25.3 24.2–26.6	25.7 25.3–26.2	26.6 26.3–27.0	27.5 26.8–28.2	+2.2	25.2 23.8–26.5	25.5 24.9–26.0	26.0 25.5–26.4	26.3 25.4–27.2	+1.1
France	24.7 23.5–26.0	25.0 24.3–25.7	25.4 24.8–26.0	25.9 25.2–26.5	+1.2	24.1 22.6–25.7	24.4 23.5–25.3	24.7 23.9–25.4	24.8 23.9–25.7	+0.7
Japan	22.1 21.4–22.8	22.4 22.1–22.7	23.1 22.9–23.3	23.5 23.1–23.9	+1.4	21.3 20.5–22.1	21.6 21.3–22.0	21.9 21.6–22.2	21.9 21.3–22.4	+0.6

Data are expressed as mean and uncertainty interval (reference 12).

^aThe difference in age-adjusted body mass index between 1980 and 2008.

consistently reported that total cholesterol is an independent risk factor for CHD.^{31,32} The relative risk of CHD associated with total cholesterol in Japan^{33,34} is similar to that reported in Western countries³⁵ as with blood pressure, smoking and diabetes.^{33,35–38} A randomized controlled trial (RCT) conducted in Japan³⁹ of the effect of statins on CHD shows a similar relative-risk reduction as reported in Western countries.⁴⁰ These lines of evidence confirm that total cholesterol is an independent risk factor in Japan.

Is the difference in CHD rates between Japan and the USA due largely to a cohort effect? We compared population-levels of total cholesterol in individuals born after WWII, that is individuals currently aged 50–69 years, between Japan and the USA (Figure 2). The current levels of total cholesterol were higher in Japan than in the USA whereas the levels were comparable 20 years ago. Thus, in this birth cohort, exposure to total cholesterol is higher in Japanese.

Some^{41,42} (including one in children⁴³) but not all⁴⁴ studies reported that levels of high-density-lipoprotein cholesterol (HDL-C) are higher in Japan than in the USA. Higher levels of HDL-C in Japanese are partly due to genetics.⁴⁵ Though low HDL-C (< 1.0 mmol/l) is considered to be a risk factor for CHD,^{46,47} the National Lipid Association has recently posed questions about protective roles of high levels of HDL-C.⁴⁶ Furthermore, little evidence exists in studies in Japan to show that high levels of HDL-C are protective against CHD⁴⁸ or atherosclerosis.⁴² Moreover, a recent study demonstrated that genetic

mechanisms that raise HDL-C do not lower the risk of CHD.⁴⁹ Thus, clinical significance of higher HDL-C in Japan remains to be elucidated.

Comparing the trends in non-HDL-C or LDL-C from 1980 through 2008 may be informative, especially because non-HDL-C is superior to total cholesterol in predicting CHD.⁵⁰ Unfortunately such data do not exist, yet it is imperative to point out that a relative risk of total cholesterol associated with CHD in Japan is similar to that in the USA at every level of total cholesterol.⁵¹ Furthermore, we have shown that among men aged 40–49 years in Japan (born after WWII), who are more exposed to Westernized lifestyle than older age groups, levels of non-HDL-C and LDL-C were similar to those in the USA, yet levels of atherosclerosis were significantly lower in Japan.⁴² Of note, prevalences of hypertension, smoking and diabetes were higher in Japan than in the USA in this study. We also compared levels of non-HDL-C and LDL-C between Japan and the USA around 2008 using the data from national surveys, and found that the levels of both non-HDL-C and LDL-C were comparable (data not shown). Therefore it is unlikely that the differences in non-HDL-C or LDL-C play a major role in explaining the low CHD mortality in Japan.

The direction and magnitude of the changes in risk factors other than total cholesterol are generally similar among these countries. One exception is smoking in men in Japan, where rates dropped by 25.5% between 1980 and 2012. One way to examine the extent the change in rates of current smokers contributes to the change in CHD mortality is to examine the difference in population-

attributable risk fraction (PARF) between 1980 and 2012.^{19,23,52} The difference in PARF in Japan, however, was very similar to that in most developed countries (Supplementary Table 3, available as Supplementary data at *IJE* online).

Obesity is a risk factor for CHD.⁵³ Much lower levels of BMI in Japan compared with Western countries may contribute to the low CHD mortality in Japan. The association of BMI with CHD, however, is largely mediated through risk factors: blood pressure, lipids and diabetes.⁵³ Levels of blood pressure have been higher in Japan than in the USA.¹¹ Japanese develop diabetes and metabolic syndrome at lower levels of BMI compared with Caucasians.^{54,55} There is no evidence that lower BMI in Japan is due to higher levels of physical activity.^{56–58} Thus the difference in BMI alone is unlikely to account for the difference in CHD mortality between Japan and the other developed countries.

These results suggest that some protective factors unique to Japanese in Japan account for their low CHD mortality. Alternatively, these results may suggest that there are higher levels of risk factors for CHD in other countries compared with Japan, such as meat intake⁵⁹ and sugar-sweetened beverages.⁶⁰ CHD mortality, however, declined during this period so that any adverse effects of these nutrients must be balanced by factors that decreased mortality.

A possible hypothesis for the difference in CHD mortality between Japan and Western countries is common source exposure in the diet that affects most of the population in Japan but is rare in Western diets. Dietary intake of fruits and vegetables,^{58,61} vitamins A, C and E and β -carotene are comparable between the USA and Japan.^{56,62} The Japanese diet compared with the US diet is relatively low in saturated fat, but very high in cholesterol, sodium and carbohydrate.^{56,62} The most likely common source in the Japanese diet is a markedly high intake of long-chain n-3 polyunsaturated fatty acids (LCn3PUFAs) and soy isoflavones.^{56,62,63} In Japan, dietary intake of LCn3PUFAs (> 1000 mg/day) is >10 times higher, and that of isoflavones (25–50 mg/day) is >20 times higher compared with in the USA.⁶⁴ LCn3PUFAs⁶⁵ and isoflavones⁶⁶ possess various biological properties related to anti-atherosclerosis. Large prospective cohort studies in Japan document that dietary intake of both LCn3PUFAs⁶⁷ and isoflavones⁶⁸ has significant inverse associations with incident CHD.

Prospective cohort studies in Western countries document that compared with little or no intake of fish, modest consumption, such as 25–30 g/day of fish, lowers CHD death rates by 20–30%⁶⁹ but not CHD incidence.^{70–72} This benefit is believed to be due to the anti-arrhythmic

properties of LCn3PUFAs.⁶⁹ In contrast, Japanese consume an average of >70 g/day of fish and studies in Japan document a significant effect of LCn3PUFAs on CHD incidence.^{67,73} Though recent RCTs of LCn3PUFAs on CHD among high-risk individuals in Western countries have all failed to show reduction in CHD,^{74–77} the doses of LCn3PUFAs administered in these RCTs, that is 300–900 mg/day, do not even reach the average dietary intake of LCn3PUFAs among the Japanese of >1000 mg/day. An RCT of LCn3PUFAs of 1800 mg/day in Japan demonstrated a significant 19% reduction in coronary events.⁷³ Importantly, the dose of 1800 mg/day was on top of their average dietary intake of >1000 mg/day. Previously we reported that serum levels of LCn3PUFAs had a significant inverse association with atherosclerosis among Japanese but not in North Americans²⁷ and that much higher levels of serum LCn3PUFAs in the Japanese significantly contributed to the cross-sectional and longitudinal difference in atherosclerosis between Japanese and Americans.^{27,78} These observations may suggest that LCn3PUFAs, at the levels that Japanese consume, have anti-atherogenic properties.⁷⁹

Limitations include ecological study in design, thus cautious interpretations are appropriate. Ecological fallacy occurs when inferences are made from group data to individual level,^{80–82} yet the current study did not infer causality at the individual level. Atherosclerosis has a long incubation period, and short-term changes in its risk factors do not necessarily translate into the change in CHD rates. Therefore we analysed the almost 30-year trend in CHD mortality and its risk factors. Data sources of risk factors are not necessarily from national surveys, yet most of these data of Japan and the USA are based on the national surveys.

In conclusion, we observed that between 1980 and 2008, age-adjusted CHD mortality in Japan declined as in other developed countries, despite a continuous and marked rise in total cholesterol in sharp contrast to a constant fall in total cholesterol in other developed countries. The lower CHD mortality in Japan compared with the USA is very unlikely to be due to the difference in trends in other CHD risk factors, cohort effects, misclassification of causes of death, competing risk with other diseases or genetics. The observation may suggest some protective factors unique to Japanese which merit further research.

Supplementary Data

Supplementary data are available at *IJE* online.

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