

Hypercholesterolemia and Lifetime Risk of Coronary Heart Disease in the General Japanese Population: Results from the Suita Cohort Study

Daisuke Sugiyama¹, Tanvir Chowdhury Turin^{2,3}, Fahmida Yeasmin³, Nahid Rumana⁴, Makoto Watanabe², Aya Higashiyama², Misa Takegami⁵, Yoshihiro Kokubo², Tomonori Okamura^{1,2} and Yoshihiro Miyamoto^{2,5}

¹Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan.

²Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan.

³Department of Family Medicine, University of Calgary, Calgary, Alberta, Canada.

⁴Foothills Medical Center, University of Calgary, Calgary, Alberta, Canada.

⁵Department of Preventive Medicine and Epidemiologic Informatics, National Cerebral and Cardiovascular Center, Osaka, Japan.

Aim: Lifetime risk (LTR) is a measure of disease burden, which presents the probability of occurrence of a specific disease in the remaining lifetime of a group of people for a given index age. This measure is useful for presenting the risk dynamics of a disease at the population level, which constitutes important public health information toward prevention. To date, there have been no studies investigating the LTR for coronary heart diseases (CHDs) in relation to hypercholesterolemia in Asian populations. Therefore, we estimated the LTR of CHDs according to serum low-density lipoprotein cholesterol (LDL-C).

Methods: The participants included in this study were 2,559 men and 2,848 women, enrolled in the Suita Cohort Study of urban residents followed up from 1989 to 2007 for a total of 69,823 person-years. We estimated the sex- and index-age-specific LTR for the first CHD event among participants with or without hypercholesterolemia (LDL-C \geq 160 mg/dL), accounting for the competing risk for mortality.

Results: For men with hypercholesterolemia, the LTR was 47.2% (95% confidence interval [CI]: 29.3–65.1%) and 44.5% (95% CI: 21.4–68.5%) for those aged 45 and 75, respectively. The LTRs of women with hypercholesterolemia were also higher than of those without hypercholesterolemia. However, their LTRs were lower for all index ages compared to men. These results did not differ for hypercholesterolemia defined by non-high-density lipoprotein cholesterol.

Conclusions: The presence of hypercholesterolemia increases the LTR for CHDs in the Japanese population, especially in men. This estimate can be used in preventive knowledge translation efforts at the population level.

See editorial vol. 27: 11-12

Key words: Lifetime risk, Coronary heart diseases, Hypercholesterolemia, Low-density lipoprotein cholesterol, Non-high-density lipoprotein cholesterol

Introduction

The incidence of and mortality resulting from coronary heart diseases (CHDs) in Japan are lower than those reported in western countries¹⁻⁴. However, owing to changes in the lifestyles and worsening of the cardiovascular risk factors, including hypercholesterol-

emia, in several studies, an increasing trend of CHDs has been reported in Japan⁵⁻⁸. Additionally, the burden of CHDs is expected to be much larger because of the increasing aging population in Japan⁹. Therefore, prevention of CHDs in Japan is imperative for public health programs. One of the major modifiable risk factors that can be targeted for the reduction of the

Address for correspondence: Daisuke Sugiyama, Department of Preventive Medicine and Public Health, School of Medicine, Keio University 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582 E-mail: dsugiyama@keio.jp

Received: January 24, 2019 Accepted for publication: April 10, 2019

Copyright©2020 Japan Atherosclerosis Society

This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

CHD risk is serum lipid profile or hypercholesterolemia.

The positive association between hypercholesterolemia and CHDs in the general Japanese population has already been described in detail in previous publications⁹⁻¹¹, and it was found in these studies that elevated serum total cholesterol (TC) significantly increased the rate of death due to CHDs. These findings were incorporated in the 10-year CHD death risk charts that were used in the Japan Atherosclerosis Society (JAS) guidelines¹²⁻¹⁴. However, younger people showed an extremely lower absolute risk compared to the absolute risk of older people by using these risk chart which predict CHD death risk with relatively shorter span. The estimation of lifetime risk (LTR), a risk projection method that accounts for the longer residual life span, provides a perspective that can complement the shorter duration risk estimation with long-term risk estimates for a better understanding of the disease burden^{15, 16}. Moreover, the effect of hypercholesterolemia on the LTR of CHDs for any Asian population has not been reported.

Aim

The aim of this study was to estimate the influence of hypercholesterolemia on short- and intermediate-term risk as well as the LTR for CHDs based upon an urban cohort in Japan.

Methods

Study Sample

The Suita Cohort Study, which was established in 1989, is a cohort study for cardiovascular diseases in the city of Suita, Osaka Prefecture, Japan. The participants of this study were randomly selected from a population aged between 30 and 79. Residents were stratified by sex and age (10-year increments), and the overall participation rate was 53.2%. The details of this study have been described in detail in previous publications¹⁷⁻²⁰. Overall, 6,483 men and women participated in the baseline survey at the National Cardiovascular Center between September 1989 and March 1994. For this analysis, participants with the following issues were excluded: lack of baseline information or loss to follow-up ($n=602$), nonfasting blood sampling ($n=280$), taking lipid-lowering drugs ($n=120$), having a history of CHD ($n=42$), and missing information on serum lipid profile ($n=32$). In total, 2,559 men and 2,848 women were included in this study (Fig. 1).

The Institutional Review Board of the National Cardiovascular Center approved this cohort study.

Informed consent was obtained from all participants at the baseline examination, and the collected data were anonymized.

Baseline Examination

Blood samples were collected from the study participants after fasting for at least 10 h. These samples were immediately centrifuged after sampling, and routine blood examinations were performed, including investigation of serum TC, high-density lipoprotein cholesterol (HDL-C), triglyceride, and glucose levels. Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula, and serum LDL-C ≥ 160 mg/dL (4.14 mmol/L) was defined as high LDL-C according to the NCEP/ATP-III criteria²¹. Non-HDL-C was calculated by subtracting HDL-C from TC, and high serum non-HDL-C ≥ 190 mg/dL (4.91 mmol/L) was defined as high non-HDL-C. Blood pressure was measured in triplicate by well-trained physicians using a standard mercury sphygmomanometer. Measurements were performed on the subjects' right arms after 5 min of rest in the seated position. The average of the second and the third measurements recorded more than 1 min apart was used²². Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or the use of antihypertensive agents. Diabetes was defined as fasting serum glucose ≥ 126 mg/dL (7.0 mmol/L) and/or the use of antidiabetic agents.

Endpoint Determination

The details of the endpoint ascertainment for the Suita Cohort Study have been reported elsewhere²³⁻²⁵. The first step of the survey for CHDs involved checking the health status of all the participants by repeated clinical visits every two years and thereafter by yearly questionnaires sent by mail or conducted over the telephone. The second step involved reviewing the in-hospital medical records of the participants who were suspected to have new-onset CHDs or those who died because of any CHD. Reviews were performed by registered hospital physicians or research physicians who were blinded to the baseline information. Definite and probable acute myocardial infarction were defined according to the criteria of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project²⁶⁻²⁸. Comprehensive systematic searches of death certificates were also performed in order to complete the surveillance for acute myocardial infarction. In addition to acute myocardial infarction, the criteria for diagnosing a CHD included sudden cardiac death within 24 h after the onset of acute symptoms and CHD followed by coronary bypass or angi-

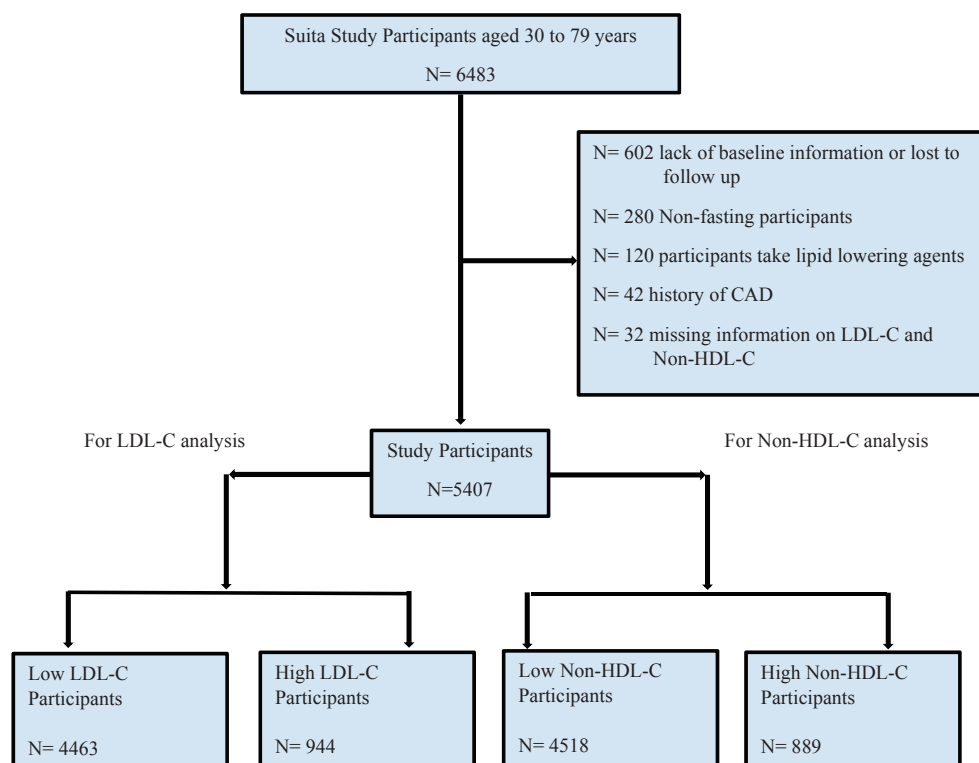


Fig. 1. Flow chart of the cohort creation

CHD: coronary heart disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

ography¹⁹).

Statistical Analysis

For the estimation of LTR, age (in years) was used as time scale and follow-up began at each patient's baseline age. Participants who were below 40 years of age at the beginning of the study period were entered into the study sample when they became 40 years old. The age categories started at the age of 40 years, and the highest age category was ≥ 90 years. The likelihood of death from a particular cause at a given time is simply the product of the overall survival until that time. The follow-up ended at CHD occurrence, death, or on December 31, 2007, depending upon which event occurred first. We estimated the cumulative CHD incidence conditional on survival to ages 45, 55, 65, and 75 years, accounting for the competing risks of death^{15, 16, 29-32}. We then utilized the competing risk adjustment to avoid risk inflation introduced in standard survival methods that do not fully account for individuals who died during follow-up because of other competing causes. A double-decrement approach was applied to take both the CHD occurrence and the all-cause mortality into consider-

ation when formulating the population at risk for each index age. Sex-specific 10-, 20-, 30-, and 40-year risks and the LTR for CHD by LDL-C or non-HDL-C categories were estimated for CHD-free participants at different index ages. Estimates were calculated using a modified survival analysis technique, as previously reported^{33, 34}. We also performed a sensitivity analysis with high LDL-C defined as ≥ 140 mg/dL. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Table 1 shows the characteristics of the participants stratified by LDL-C levels at baseline. At baseline, 12.5% of the men and 22.0% of the women had high LDL-C, whereas 14.1% of the men and 18.6% of the women had high non-HDL-C. During the 69,823 person-years of follow-up, 124 men and 57 women were diagnosed with CHD. **Table 2** displays the 10-, 20-, 30-, and 40-year risks as well as the LTR of CHDs based on the LDL-C categories for men and women of various index ages. The person-year of follow-up, incidence of CHD, and mortality due to

Table 1. Characteristics of study participants

	Variables	LDL-C categories	
		Low (LDL-C < 160)	High (LDL-C ≥ 160)
Men	Number of subjects	2240	319
	Age, years (s.d)	55.7 (13.4)	56.6 (12.1)
	LDL-C, mg/dL (s.d)	115.8 (26.7)	178.2 (17.2)
	HDL-C, mg/dL (s.d)	49.4 (13.5)	46.6 (10.6)
	Non-HDL-C, mg/dL (s.d)	144.1 (29.1)	206.8 (20.4)
	BMI, kgm ⁻² (s.d)	22.7 (2.9)	23.5 (2.8)
	Waist circumference, cm (s.d)	82.4 (8.1)	84.0 (7.8)
	Systolic blood pressure, mmHg (s.d)	128.2 (20.9)	129.6 (20.0)
	Diastolic blood pressure, mmHg (s.d)	79.0 (12.2)	80.3 (11.1)
	Hypertension, <i>n</i> (%)	723 (32.3)	117 (36.7)
	Diabetes, <i>n</i> (%)	130 (5.8)	21 (6.6)
	Smoking, <i>n</i> (%)		
	Never smoker	420 (18.8)	63 (19.8)
	Current smoker	1124 (50.2)	154 (48.3)
	Ex-smoker	664 (29.6)	97 (30.4)
	Unknown	32 (1.4)	5 (1.6)
	Drinking, <i>n</i> (%)		
	Never drinker	453 (20.2)	83 (26.0)
	Current drinker	1671 (74.6)	216 (67.7)
	Ex-drinker	86 (3.8)	16 (5.0)
Unknown	30 (1.3)	4 (1.3)	
Women	Number of subjects	2223	625
	Age, years (s.d)	52.5 (13.1)	58.7 (10.0)
	LDL-C, mg/dL (s.d)	120.9 (23.7)	183.9 (22.8)
	HDL-C, mg/dL (s.d)	57.4 (13.7)	53.9 (12.1)
	Non-HDL-C, mg/dL (s.d)	141.2 (27.8)	208.8 (28.1)
	BMI, kgm ⁻² (s.d)	22.0 (3.2)	23.1 (3.3)
	Waist circumference, cm (s.d)	76.5 (10.1)	80.4 (10.1)
	Systolic blood pressure, mmHg (s.d)	122.4 (21.5)	130.7 (21.0)
	Diastolic blood pressure, mmHg (s.d)	74.2 (11.8)	78.5 (11.6)
	Hypertension, <i>n</i> (%)	511 (23.0)	238 (38.1)
	Diabetes, <i>n</i> (%)	69 (3.1)	30 (4.8)
	Smoking, <i>n</i> (%)		
	Never smoker	1826 (82.1)	505 (80.8)
	Current smoker	269 (12.1)	70 (11.2)
	Ex-smoker	80 (3.6)	23 (3.7)
	Unknown	48 (2.2)	27 (4.3)
	Drinking, <i>n</i> (%)		
	Never drinker	1389 (62.5)	428 (68.5)
	Current drinker	748 (33.7)	166 (26.6)
	Ex-drinker	41 (1.8)	8 (1.3)
Unknown	45 (2.0)	23 (3.7)	

LDL-C: low-density lipoprotein cholesterol, s.d: standard deviation, HDL-C: high-density lipoprotein cholesterol, BMI: body mass index

Table 2. Person-years of follow-up and number of events (CHD and Death) by sex and LDL-C Categories

	Age Group (Years)														
	30-44			45-54			55-64			65-74			75-100		
	PY	CHD	Death	PY	CHD	Death	PY	CHD	Death	PY	CHD	Death	PY	CHD	Death
Men															
Low LDL-C	7,616	3	10	6,142	10	23	7,356	29	116	5,203	39	217	1,307	15	100
High LDL-C	850	2	0	960	4	3	1,315	10	12	834	7	21	134	5	11
Women															
Low LDL-C	10,302	1	8	7,055	4	15	6,952	8	49	4,297	14	79	1,093	7	42
High LDL-C	756	0	2	2,257	2	7	3,112	8	15	2,012	11	31	277	2	13

LDL-C: low-density lipoprotein cholesterol, CHD: coronary heart disease, PY: person-years

Serum LDL-C < 160 mg/dL was defined as "Low LDL-C".

Serum LDL-C ≥ 160 mg/dL was defined as "High LDL-C".

Table 3. Person-years of follow-up and number of events (CHD and Death) by sex and non-HDL-C Categories

	Age Group (Years)														
	30-44			45-54			55-64			65-74			75-100		
	PY	CHD	Death	PY	CHD	Death	PY	CHD	Death	PY	CHD	Death	PY	CHD	Death
Men															
Low non-HDL-C	7,363	1	10	6,018	10	22	7,224	26	111	5,259	35	219	1,304	15	96
High non-HDL-C	1,103	4	0	1,084	4	4	1,447	13	17	778	11	19	137	5	15
Women															
Low non-HDL-C	10,607	1	8	7,551	4	17	7,316	7	55	4,487	15	81	1,111	8	40
High non-HDL-C	452	0	2	1,761	2	5	2,748	9	9	1,822	10	29	259	1	15

HDL-C: high-density lipoprotein cholesterol, CHD: coronary heart disease, PY: person-years

Serum non-HDL-C < 190 mg/dL was defined as "Low non-HDL-C".

Serum non-HDL-C ≥ 190 mg/dL was defined as "High non-HDL-C".

CHD across the age groups are shown in [Table 2](#) for the LDL-C categories and in [Table 3](#) for the non-HDL-C categories.

The estimated LTR of CHDs, accounting for the competing risk of death, at 45 years of age was 13.7% (95% confidence interval [CI]: 10.9–16.5%) for men with low LDL-C and 47.2% (95% CI: 29.3–56.1%) for men with high LDL-C ([Table 4](#)). For women at the index age of 45 years, the estimated LTR of CHDs for low and high LDL-C was 7.1% (95% CI: 4.4–9.8%) and 10.2% (95% CI: 5.6–14.8%) for low and high LDL-C, respectively. For both sexes, the estimated intermediate-term risks (10, 20, 30, and 40 years) increased across time. However, the estimated LTRs in men were lower with higher index ages, whereas in women, they were nearly constant regardless of the index age.

[Table 5](#) shows the 10-, 20-, 30-, and 40-year risks as well as the LTR of CHDs based on the non-HDL-C categories for men and women of various

index ages; these results were similar to those for the LDL-C categories.

The results of the sensitivity analysis with high LDL-C defined as ≥ 140 mg/dL showed that the estimated LTRs for CHDs, in both men and women, were smaller than the ones where high LDL-C was defined as ≥ 160 mg/dL. The estimated LTRs of men with high LDL-C were 28.0% (95% CI: 16.5–39.6%) at the index age of 45 years and 22.8% (95% CI: 7.7–37.9%) at the index age of 75 years. In women with high LDL-C, the estimated LTRs were 8.1% (95% CI: 5.1–11.2%) at the index age of 45 years and 5.8% (95% CI: 2.7–8.9%) at the index age of 75 years.

Discussion

In this urban-community-based cohort in Japan, we observed that the LTR of CHDs was affected by hypercholesterolemia in middle-aged men and women. Individuals with low LDL-C or non-HDL-C

Table 4. Age and sex-specific 10-, 20-, 30- and 40-year and lifetime risk estimates for coronary heart disease based on low-density lipoprotein cholesterol level (adjusted for the competing risk of death)

Sex	Index age (yrs)	Short and intermediate term risk (Yrs)	LDL-C Categories	
			Low LDL-C	High LDL-C
Men	45	10	0.5 (0.0-1.0)	3.7 (0.0-7.9)
		20	2.8 (1.6-4.0)	8.5 (3.1-14.0)
		30	6.0 (4.4-7.6)	14.2 (8.0-20.5)
		40	10.6 (8.4-12.7)	20.2 (12.9-27.5)
		LTR	13.7 (10.9-16.5)	47.2 (29.3-65.1)
	55	10	2.4 (1.3-3.4)	5.1 (1.1-9.2)
		20	5.6 (4.1-7.2)	11.2 (5.8-16.6)
		30	10.3 (8.2-12.4)	17.6 (10.8-24.4)
		LTR	13.5 (10.6-16.3)	40.4 (27.5-65.2)
	65	10	3.6 (2.3-4.8)	6.6 (2.4-10.8)
		20	8.6 (6.6-10.7)	13.5 (7.1-19.8)
		LTR	12.0 (9.2-14.9)	44.7 (24.5-64.9)
	75	10	6.4 (4.4-8.5)	8.1 (2.2-14.1)
		LTR	10.7 (7.4-14.0)	45.0 (21.4-68.5)
	Women	45	10	0.5 (0.0-1.0)
20			0.6 (0.1-1.2)	0.7 (0.0-1.6)
30			1.4 (0.6-2.3)	3.9 (1.8-6.0)
40			4.7 (3.0-6.4)	8.9 (5.0-12.8)
LTR			7.1 (4.4-9.8)	10.2 (5.6-14.8)
55		10	0.1 (0.0-0.4)	0.7 (0.0-1.6)
		20	1.0 (0.3-1.7)	4.0 (1.9-6.1)
		30	4.3 (2.6-6.0)	9.2 (5.2-13.2)
		LTR	6.7 (4.0-9.4)	10.5 (5.8-15.2)
65		10	0.9 (0.2-1.6)	3.5 (1.4-5.5)
		20	4.3 (2.6-6.0)	8.9 (4.8-13.0)
		LTR	6.8 (4.1-9.6)	10.3 (5.4-15.2)
75		10	3.7 (2.0-5.4)	5.9 (2.0-9.9)
		LTR	6.4 (3.5-9.3)	7.5 (2.6-12.4)

LDL-C: low-density lipoprotein cholesterol, LTR: lifetime risk
 Serum LDL-C < 160 mg/dL was defined as "Low LDL-C".
 Serum LDL-C ≥ 160 mg/dL was defined as "High LDL-C".

had a lower LTR of CHDs than those with high LDL-C or non-HDL-C. For all index ages, the LTR of CHDs was higher in men than in women. This is the first study describing the relationship between hypercholesterolemia and LTR of CHDs in Asian populations. There is currently no report comparing directly the incident of CHDs between Japan and other countries, including Asian countries, using the same definition of CHDs. However, Steg *et al.* showed that the one-year event rates of nonfatal myocardial infarction were almost the same between Japan and Asia in the Reduction of Atherothrombosis for Continued Health Registry (REACH registry)³⁵. We think our results may be useful to not only Japan, but also other Asian countries.

We previously reported on the LTR of CHDs from the Suita Cohort Study among individuals with and without hypertension and with and without diabetes mellitus^{36,37}. At 45 years of age, the competing-risk-adjusted LTR of CHDs was 14.1% and 27.0% for normotensive and hypertensive men, respectively; 6.2% and 14.9% for normotensive and hypertensive women, respectively; 21.1% and 16.7% for men with and without diabetes, respectively; and 14.2% and 9.2% for women with and without diabetes, respectively. When compared to other risk factors, the estimated LTRs of CHDs were very high in men (approximately 45%) and low in women (approximately 11%) with hypercholesterolemia. In most Japanese community-based cohort studies, hypercholesterol-

Table 5. Age and sex-specific 10-, 20-, 30- and 40-year and lifetime risk estimates for coronary heart disease based on Non-high-density lipoprotein cholesterol level (adjusted for the competing risk of death)

Sex	Index age (yrs)	Short and intermediate term risk (Yrs)	Non-HDL-C Categories	
			Low Non-HDL-C	High Non-HDL-C
Men	45	10	0.2 (0.0-0.5)	5.1 (0.7-9.5)
		20	2.5 (1.4-3.7)	9.2 (3.9-14.4)
		30	5.2 (3.7-6.8)	17.3 (11.0-23.6)
		40	9.5 (7.5-11.6)	25.2 (17.6-32.9)
		LTR	12.7 (9.9-15.4)	41.45 (25.0-57.7)
	55	10	2.4 (1.3-3.5)	4.3 (0.9-7.7)
		20	5.2 (3.7-6.7)	13.1 (7.7-18.5)
		30	9.5 (7.5-11.6)	21.7 (14.4-28.9)
		LTR	12.7 (9.9-15.6)	39.9 (21.7-56.4)
	65	10	3.0 (1.8-4.2)	9.5 (4.8-14.3)
		20	7.7 (5.7-9.7)	18.8 (11.5-26.1)
		LTR	11.2 (8.3-14.0)	37.7 (19.1-56.3)
	75	10	5.9 (3.9-7.9)	11.6 (4.3-19.0)
		LTR	10.2 (7.0-13.5)	35.3 (12.5-58.2)
	Women	45	10	0.5 (0.0-0.9)
20			0.6 (0.1-1.1)	0.8 (0.0-1.9)
30			1.3 (0.5-2.0)	4.7 (2.3-7.2)
40			4.9 (3.1-6.6)	9.1 (5.0-13.1)
LTR			7.2 (4.5-9.9)	10.5 (5.6-15.3)
55		10	0.1 (0.0-0.4)	0.8 (0.0-2.0)
		20	0.8 (0.2-1.4)	4.9 (2.4-7.4)
		30	4.5 (2.7-6.2)	9.4 (5.2-13.6)
		LTR	6.9 (4.2-9.6)	10.9 (5.9-15.9)
65		10	0.7 (0.1-1.3)	4.3 (1.9-6.6)
		20	4.5 (2.7-6.3)	8.9 (4.7-13.2)
		LTR	7.0 (4.2-9.8)	10.5 (5.4-15.6)
75		10	4.1 (2.3-5.9)	5.2 (1.2-9.2)
		LTR	6.8 (3.8-9.7)	6.9 (1.8-12.0)

HDL-C: high-density lipoprotein cholesterol, LTR: lifetime risk
 Serum non-HDL-C < 190 mg/dL was defined as "Low non-HDL-C".
 Serum non-HDL-C ≥ 190 mg/dL was defined as "High non-HDL-C".

emia is strongly related to CHDs but weakly related to stroke, as shown in the JAS guidelines¹⁴. On the other hand, hypertension and diabetes are related to stroke as well as CHDs^{14, 38, 39}. Diabetes is also associated with cancer⁴⁰. In general, the LTR for a targeted disease is calculated by the accumulation of cases among a population, excluding deaths due to other reasons, and this adjustment is known to be the one of competing risk, and this approach is essential for estimating the LTR^{16, 31, 32}. Therefore, the LTR of a disease due to a risk factor, which can be associated with various other diseases, will be influenced by the exposure (the risk factor of interest) and outcome (disease of interest) relationship. Actually, if high LDL-C is defined by serum LDL-C ≥ 140 mg/dL, the estimated

LTR of high LDL-C for CHDs in men will be 22.8%, which is smaller than the one defined by serum LDL-C ≥ 160 mg/dL (45.0%). This discrepancy, to some extent, can be attributed to the difference between the numbers of deaths in the age group 75–100 with high LDL-C defined by ≥ 140 mg/dL and ones with high LDL-C defined by ≥ 160 mg/dL. The number of CHDs in the high LDL-C category was almost similar (seven events defined by ≥ 140 mg/dL and five events defined by ≥ 160 mg/dL), but the number of deaths in the high LDL-C category defined by ≥ 140 mg/dL was observed much more than the one defined by 160 mg/dL (29 events versus 11 events, respectively).

There is very limited evidence regarding the LTR

of CHDs in relation to hypercholesterolemia. In one previous study based upon the Framingham Heart Study (FHS)⁴¹⁾, it was reported that, at 40 years of age, the LTRs of CHDs were 57.3% and 32.9% for men and women with high TC (serum TC \geq 240 mg/dL, which is thought to be equivalent to LDL-C \geq 160 mg/dL and non-HDL-C \geq 190 mg/dL), respectively. The estimated LTR for men was very similar to that reported in our study; however, in women, the estimated LTR in the FHS was much larger than that reported in our study. In Japan, the influence of hypercholesterolemia on CHDs has been reported to be quite different across men and women. The results from National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980 (NIPPON DATA80)^{9, 42)} showed that the risk of CHDs linearly increased over TC 200 mg/dL in men; however, there was no association below TC 260 mg/dL in women. Therefore, the difference of LTR between men and women may be larger in Japan than in western countries.

The guidelines for CHD prevention adopted the estimated 10-year risk for CHD onset or death based upon the findings of cohort studies with long-term follow-up periods, such as the NIPPON DATA80¹²⁾, the Suita Study¹⁹⁾, and the FHS⁴³⁾. However, the estimated 10-year risks were very low in the younger population, particularly in women, so it is difficult to motivate such individuals to make lifestyle improvements for the prevention of CHDs. On the other hand, LTR is an indicator that can be easily interpreted. For example, based upon our results, the probability of new CHD onset for a 45-year-old man with hypercholesterolemia is 47.2% in his remaining life. Therefore, LTR can be useful in promoting health-oriented motivation for the prevention of atherosclerotic cardiovascular diseases (ASCVDs) through lifestyle modification and/or medication. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the Assessment of Cardiovascular Risk showed the LTR of ASCVDs for a population aged 20–59, who were free from ASCVD and were not at a high short-term risk⁴⁴⁾. However, there are no applications for the Asian population, including Japan, so we must establish guidelines for the prevention of ASCVDs utilizing LTR.

The major strength of our study is the uniqueness of the study cohort. This is an urban-population-based cohort in Japan. Moreover, the prospective ascertainment of the endpoints using standardized and previously validated clinical diagnostic criteria contributed to the accurate confirmation of outcomes including CHD and deaths²³⁻²⁵⁾.

There are a few limitations that need to be kept in mind while utilizing the results of this study. First, we had a small number of CHD events as outcomes. Because of this small number of CHD events, we could not perform more detailed analyses (e.g., using three or more categories for LDL-C or non-HDL-C or combinations of other major risk factors) for the determination of LTRs of CHDs. The small number of CHD events also affected the LTR estimates. The CIs of the estimates for the high LDL-C and high non-HDL-C are quite wide and are reflective of less stable estimates even when taking a conservative approach. We acknowledge the need for further studies based upon a pooled analysis of the larger cohorts in the future. Second, the Suita Cohort is based on an urban population, so the estimates in this study may not represent the overall Japanese population, thus impacting the external validity of our study. However, there is a high urbanization rate in Japan, and most of the changes in lifestyle factors associated with the risk for CHDs are thought to be due to urbanization^{2, 3, 45, 46)}. Therefore, we believe that our findings of high LTRs of CHDs in an urban population are representative of a large proportion of the Japanese population.

Conclusions

In conclusion, the presence of hypercholesterolemia increases the LTR for CHDs in the Japanese population, especially in men. These estimates can be used for preventive knowledge translation efforts at the population level.

Conflict of Interest

The authors have no conflicts of interest.

Financial Support

This study was supported by the Intramural Research Fund (27-4-3) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center, Comprehensive Research on Cardiovascular and Lifestyle Related Diseases: H29-Junkankitou [Seishuu]-Ippan-003) and a Grant-in-Aid for Young Scientists B 17K15834 from the Japan Society for the Promotion of Science

Acknowledgments

We thank the members of the Suita City Health Center, the Suita Medical Association, and all of the researchers and staff of the Department of Preventive Cardiology for performing the medical examinations

and follow-ups. We also thank Satsuki-Junyukai and the volunteers involved in the administration of the Suita Cohort Study.

References

- 1) Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. *World Health Stat Q*, 1987; 41: 155-178
- 2) Ueshima H. Trends in Asia. In: M.G Marmot, P. Elliott (eds), *Coronary Heart Disease Epidemiology: From Aetiology to Public Health*, Oxford University Press, New York, USA, 2005; 102-113
- 3) Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in asia: a selected review. *Circulation*, 2008; 118: 2702-2709
- 4) Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. *J Atheroscler Thromb*, 2007; 14: 278-286
- 5) Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, Tomioka N, Okayama A, Nakamura Y, Abbott RD, Ueshima H. Trend of increase in the incidence of acute myocardial infarction in a Japanese population: Takashima AMI registry, 1990-2001. *Am J Epidemiol*, 2008; 167: 1358-1364
- 6) Kitamura A, Iso H, Iida M, Naito Y, Sato S, Jacobs DR, Nakamura M, Shimamoto T, Komachi Y. Trends in the incidence of coronary heart disease and stroke and the prevalence of cardiovascular risk factors among Japanese men from 1963 to 1994. *Am J Med*, 2002; 112: 104-109
- 7) Takii T, Yasuda S, Takahashi J, Ito K, Shiba N, Shirato K, Shimokawa H, MIYAGI-AMI Study Investigators. Trends in acute myocardial infarction incidence and mortality over 30 years in Japan: report from the Miyagi-AMI Registry Study. *Circ J*, 2010; 74: 93-100
- 8) Nishiyama S, Watanabe T, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Nitobe J, Shibata Y, Konta T, Kawata S, Kato T, Fukao A, Kubota I. Trends in coronary risk factors among patients with acute myocardial infarction over the last decade: the Yamagata AMI Registry. *J Atheroscler Thromb*, 2010; 17: 989-998
- 9) Sugiyama D, Okamura T, Watanabe M, Higashiyama A, Okuda N, Nakamura Y, Hozawa A, Kita Y, Kadota A, Murakami Y, Miyamatsu N, Ohkubo T, Hayakawa T, Miyamoto Y, Miura K, Okayama A, Ueshima H; NIPPON DATA 80/90 Research Group. Risk of hypercholesterolemia for cardiovascular disease and the population attributable fraction in a 24-year Japanese cohort study. *J Atheroscler Thromb*, 2015; 22: 95-107
- 10) Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H; Japan Arteriosclerosis Longitudinal Study Group. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events -the JALS-ECC-. *Circ J*, 2010; 74: 1346-1356
- 11) Nagasawa SY, Okamura T, Iso H, Tamakoshi A, Yamada M, Watanabe M, Murakami Y, Miura K, Ueshima H; Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. *J Am Heart Assoc*, 2012; 1: e001974
- 12) NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J*, 2006; 70: 1249-1255
- 13) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K; Japan Atherosclerosis Society. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. *J Atheroscler Thromb*, 2013; 20: 517-523
- 14) Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, Umemoto S, Egusa G, Ohmura H, Okamura T, Kihara S, Koba S, Saito I, Shoji T, Daida H, Tsukamoto K, Deguchi J, Dohi S, Dobashi K, Hamaguchi H, Hara M, Hiro T, Biro S, Fujioka Y, Maruyama C, Miyamoto Y, Murakami Y, Yokode M, Yoshida H, Rakugi H, Wakatsuki A, Yamashita S; Committee for Epidemiology and Clinical Management of Atherosclerosis. Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. *J Atheroscler Thromb*, 2018; 25: 846-984
- 15) Turin TC, Hemmelgarn BR. Long-term risk projection and its application to nephrology research. *J Nephrol*, 2012; 25(4): 441-449
- 16) Satoh M, Ohkubo T, Asayama K, Murakami Y, Sugiyama D, Yamada M, Saitoh S, Sakata K, Irie F, Sairenchi T, Ishikawa S, Kiyama M, Ohnishi H, Miura K, Imai Y, Ueshima H, Okamura T; on behalf of the EPOCH-JAPAN Research Group. Lifetime Risk of Stroke and Coronary Heart Disease Deaths According to Blood Pressure Level EPOCH-JAPAN (Evidence for Cardiovascular Prevention From Observational Cohorts in Japan). *Hypertension*, 2019; 73: 52-59
- 17) Tsukinoki R, Okamura T, Watanabe M, Kokubo Y, Higashiyama A, Nishimura K, Takegami M, Murakami Y, Okayama A, Miyamoto Y. Blood pressure, low-density lipoprotein cholesterol and incidences of coronary artery disease and ischemic stroke in Japanese: the Suita study. *Am J Hypertens*, 2014; 27: 1362-1369
- 18) Arai H, Kokubo Y, Watanabe M, Sawamura T, Ito Y, Minagawa A, Okamura T, Miyamoto Y. Small dense low-density lipoproteins cholesterol can predict incident cardiovascular disease in an urban Japanese cohort: the Suita study. *J Atheroscler Thromb*, 2013; 20: 195-203
- 19) Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the Framingham risk score: the Suita study. *J Atheroscler Thromb*, 2014; 21: 784-798
- 20) Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Ono Y, Nishimura K, Okayama A, Miyamoto Y. A revised definition of the metabolic syndrome predicts coronary artery disease and ischemic stroke after adjusting for low density lipoprotein cholesterol in a 13-year cohort study of Japanese: the Suita study. *Atherosclerosis*, 2011; 217: 201-206

- 21) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*, 2001; 285: 2486-2497
- 22) Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension*, 2008; 52: 652-659
- 23) Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study. *Atherosclerosis*, 2009; 203: 587-592
- 24) Higashiyama A, Okamura T, Ono Y, Watanabe M, Kokubo Y, Okayama A. Risk of smoking and metabolic syndrome for incidence of cardiovascular disease--comparison of relative contribution in urban Japanese population: the Suita study. *Circ J*, 2009; 73: 2258-2263
- 25) Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Ono Y, Miyamoto Y, Yoshimasa Y, Okayama A. Triglycerides and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort: the Suita study. *Atherosclerosis*, 2010; 209: 290-294
- 26) World Health Organization. Document for meeting of MONICA Principal Investigators. In: WHO, editors. Geneva, Switzerland: MONICA Project: Event Registration Data Component, MONICA Manual. Version 1.1. 1986; S-4: 9-11
- 27) Ministry of Health and Welfare. Study Project of Monitoring System for Cardiovascular Disease Commissioned by the Ministry of Health and Welfare: Manual for the Registry and Follow-Up of Ischemic Heart Disease, National Cardiovascular Center, Osaka, Japan, 1998
- 28) Ministry of Health and Welfare. Study Project of Monitoring System for Cardiovascular Disease Commissioned by the Ministry of Health and Welfare: Manual for the Registry and Follow-Up of Stroke, National Cardiovascular Center, Osaka, Japan, 1998
- 29) Beiser A, D'Agostino RB Sr, Seshadri S, Sullivan LM, Wolf PA. Computing estimates of incidence, including lifetime risk: Alzheimer's disease in the Framingham study. The practical incidence estimators (pie) macro. *Stat Med*, 2000; 19: 1495-1522
- 30) Turin TC, Tonelli M, Manns BJ, Ahmed SB, Ravani P, James M, Hemmelgarn BR. Lifetime risk of ESRD. *J Am Soc Nephrol*, 2012; 23: 1569-1578
- 31) Turin TC, Kokubo Y, Murakami Y, Higashiyama A, Rumana N, Watanabe M, Okamura T. Lifetime risk of stroke in Japan. *Stroke*, 2010; 41: 1552-1554
- 32) Turin TC, Kokubo Y, Murakami Y, Higashiyama A, Rumana N, Watanabe M, Okamura T. Lifetime risk of acute myocardial infarction in Japan. *Circ Cardiovasc Qual Outcomes*, 2010; 3: 701-703
- 33) Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men. *JAMA*, 2002; 287: 1003-1010
- 34) Driver JA, Djoussé L, Logroscino G, Gaziano JM, Kurth T. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. *BMJ*, 2008; 337: a2467
- 35) Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, Liao CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*, 2007; 297: 1197-1206
- 36) Turin TC, Okamura T, Afzal RA, Rumana N, Watanabe M, Higashiyama A, Nakao YM, Nakai, Takegami M, Nishimura K, Kokubo Y, Okayama A, Miyamoto Y. Impact of hypertension on the lifetime risk of coronary heart disease. *Hypertens Res*, 2016; 39: 548-551
- 37) Turin TC, Okamura T, Rumana N, Afzal AR, Watanabe M, Higashiyama A, Nakao YM, Nakai M, Takegami M, Nishimura K, Kokubo Y, Okayama A, Miyamoto Y. Diabetes and lifetime risk of coronary heart disease. *Prim Care Diabetes*, 2017; 11: 461-466
- 38) Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, Ueshima H; Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. *Hypertens Res*, 2012; 35: 947-953
- 39) Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, Ohira T, Yamagishi K, Iida M, Shimamoto T. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. *Diabetologia*, 2004; 47: 2137-2144
- 40) Sasazuki S, Charvat H, Hara A, Wakai K, Nagata C, Nakamura K, Tsuji I, Sugawara Y, Tamakoshi A, Matsuo K, Oze I, Mizoue T, Tanaka K, Inoue M, Tsugane S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Cancer Sci. Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan, 2013; 104: 1499-1507
- 41) Lloyd-Jones DM, Wilson PW, Larson MG, Leip E, Beiser A, D'Agostino RB, Cleeman JI, Levy D. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. *Arch Intern Med*, 2003; 163: 1966-1972
- 42) Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H; NIPPON DATA80 Research Group. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis*, 2007; 190: 216-223
- 43) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*, 1998; 97: 1837-1847
- 44) Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American

- College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, 2014; 129: S49-73
- 45) Okayama A, Ueshima H, Marmot M, Elliott P, Choudhury SR, Kita Y. Generational and regional differences in trends of mortality from ischemic heart disease in Japan from 1969 to 1992. *Am J Epidemiol*, 2001; 153: 1191-1198
- 46) https://www.estat.go.jp/statsearch/files?page=1&layout=detail&toukei=00200523&tstat=00000070001&cycle=0&tclass1=00001051218&stat_infid=000031589250&second2=1