Fig. 1

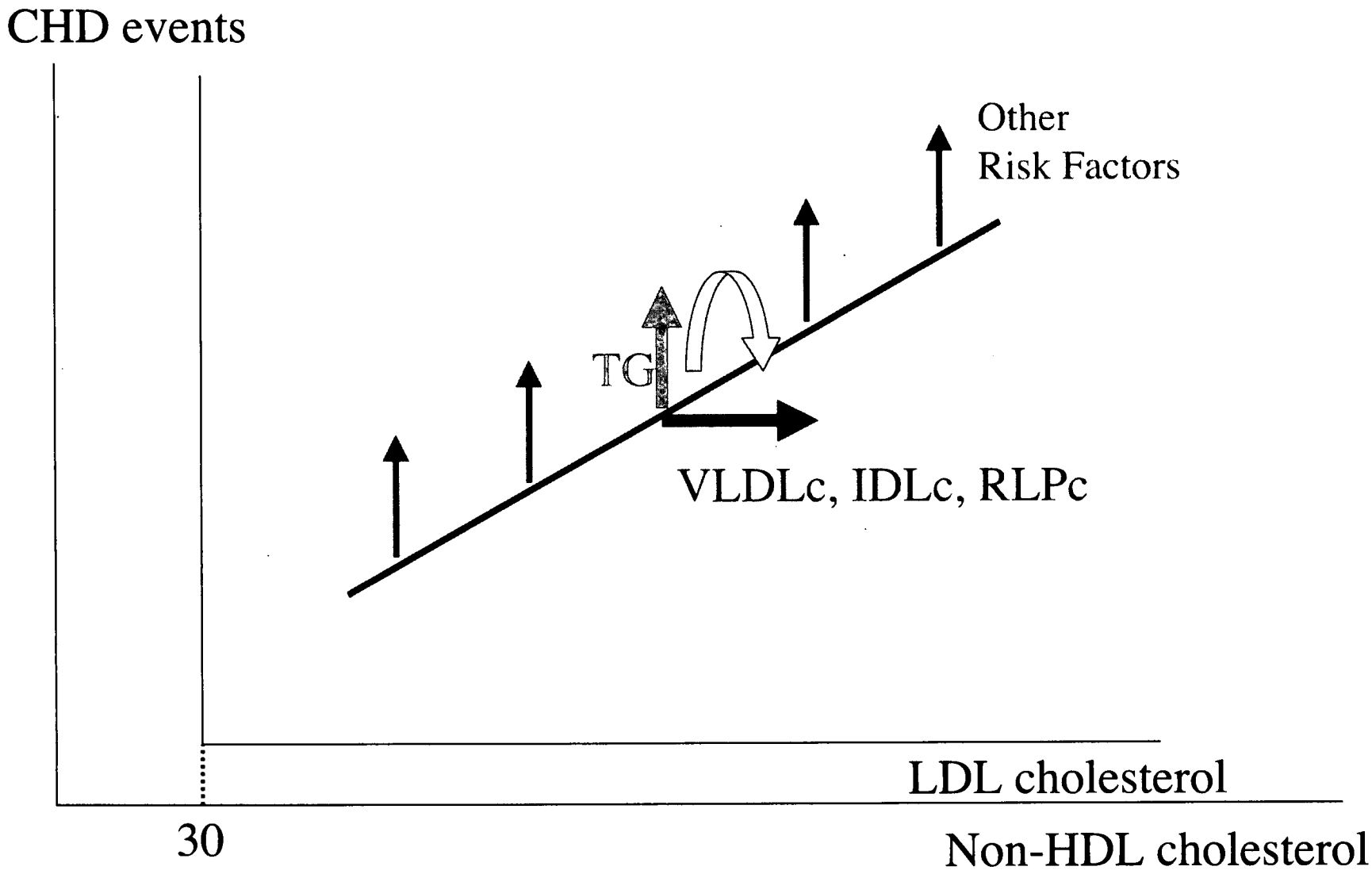
CHD events
Other
Risk Factors
TG
VLDLc, IDLc, RLPc
LDL cholesterol
30
Non-HDL cholesterol

Fig. 2

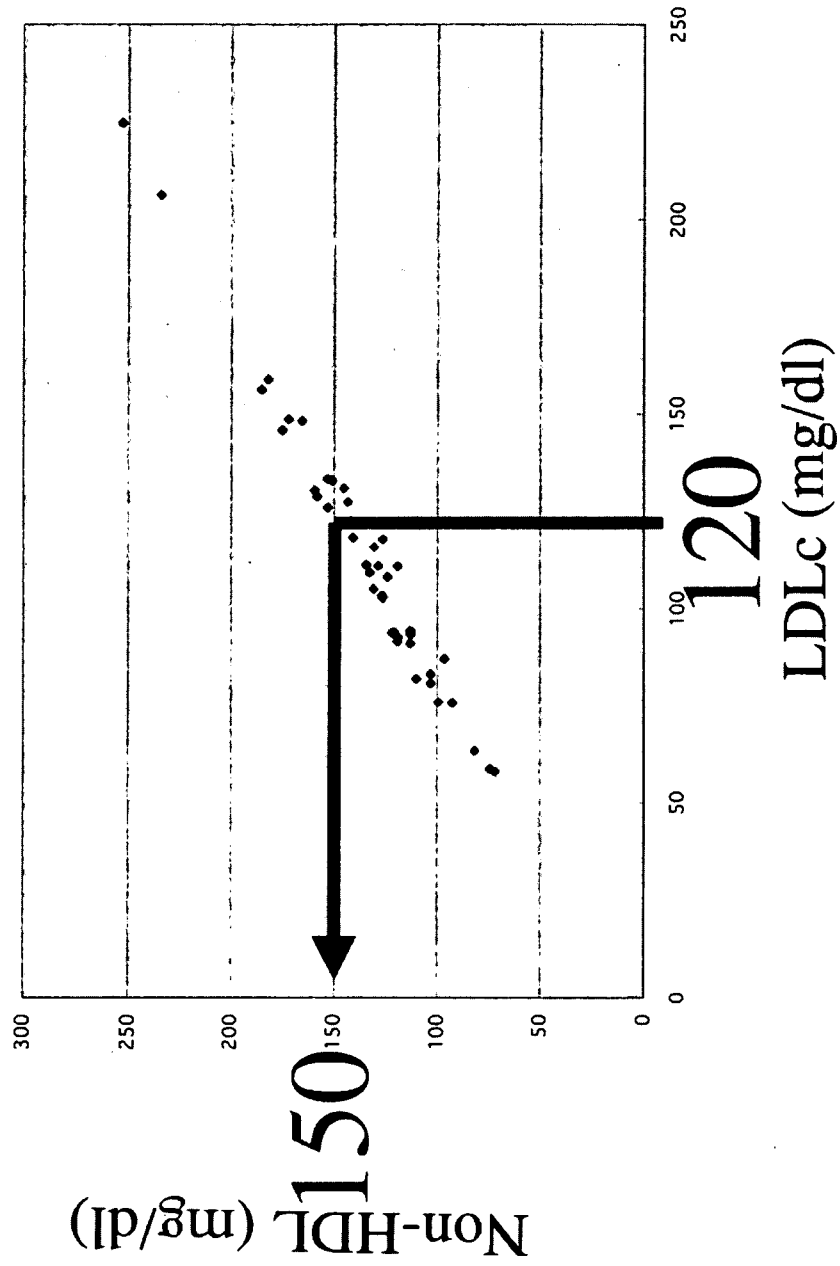
Non-HDL (mg/dl)
150
120
LDLc (mg/dl)
300
250
200
150
100
50
0
250
200
150
100
50
0

Fig. 3

GuideLines for patients with hypertriglyceridemia

Treatment	Categories		Goal for plasma lipids (mg/dL)		
		Coronary Risk Factors other than LCL-C	Primiary LDL-C	Secondary nonHDL-C	HDL-C
Primary Prevention Improving lifestyle as the first line, followed by medication	I (Low Risk Group)	0	<160	**<190**	≥ 40
	II (Intermediate)	1～2	<140	**<170**	
	III (High)	≥ 3	<120	**<150**	
Secondary Prevention Improving life-style&medication	Past History of CHD		<100	**<130**	

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Diabetes Research and Clinical Practice 77S (2007) S23–S29
DIABETES RESEARCH AND CLINICAL PRACTICE
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Cross-sectional association between BMI, glycemic control and energy intake in Japanese patients with type 2 diabetes Analysis from the Japan Diabetes Complications Study

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Accepted 29 January 2007
Available online 23 May 2007

Abstract

Although, weight loss is associated with improved glycemic control in diabetic patients, the relationships between patient weight, daily energy intake (EI), and glycemic or other control status have been poorly investigated. Baseline characteristics of the Japan Diabetes Complications Study, a representative cohort of Japanese diabetic patients, were used for quartile analysis stratified according to patient body mass index (BMI) and EI. Despite a 1.4-fold discrepancy in BMI between the highest and the lowest quartiles, no significant linear trend in HbA_{1C} levels or EI between quartiles was seen, although, waist/hip ratio, blood pressure, total cholesterol and triglycerides increased and HDL cholesterol decreased with the increase in BMI. Quartile analysis, according to EI, revealed a 1.8-fold elevation in EI between the lowest and the highest quartile. Nevertheless, the differences in patient BMI between the lowest and the highest quartile were no more than 3% and there were no significant linear trends among the four quartiles in most parameters including HbA_{1C}, blood pressure, serum lipids. These results revealed only very limited cross-sectional correlations among BMI, EI and other parameters suggesting that it is necessary to consider much wider variations in ideal weight and optimal dietary prescription when making assessments of diabetic patients.

Keywords: Body mass index; Energy intake; Glycemic control; Japan Diabetes Complications Study (JDCS)

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0168-8227/$ – see front matter © 2007 Published by Elsevier Ireland Ltd.
doi:10.1016/j.diabres.2007.01.029

1. Introduction

Obesity increases morbidity and mortality in patients with type 2 diabetes and short-term studies have demonstrated that even moderate weight reduction through diet and/or exercise can improve patient hyperglycemia [1–3]. However, the few long-term cohort studies on the effects of weight loss on glycemic control in diabetic patients produced inconsistent results [2–5]. It has been speculated that the inconsistencies may have arisen from the confounding effects of other influences on body weight, such as the disease process itself or the medications used [6,7]. Even the detailed cross-sectional relationships between body weight and glycemic control indices in type 2 diabetic patients have been poorly investigated in large-scale settings, and the clinical utility of patient body weight and energy intake data has yet to be fully evaluated. To deepen our understanding of obesity in diabetic patients, further analysis of patient data obtained from the Japan Diabetes Complications Study (JDCS) was performed to clarify the cross-sectional relationships between obesity, energy intake and diabetes control status within a single ethnic group.

2. Patients and methods

The JDCS is a nationwide prospective study of the characteristics of 2205 Japanese patients with type 2 diabetes aged between 40 and 70 years old at registration [8–12]. All patients had been previously diagnosed with type 2 diabetes, having glycohaemoglobin A_{1C} levels of more than 6.5%. Patients with impaired glucose tolerance were not included in this study. Other characteristics of the patients and details of the protocol were described previously [8]. The protocol received ethical approval from the committee of the Ministry of Health and Welfare, Japan and written informed consent was obtained from all patients enrolled. From the study cohort, we analysed the baseline data from 1637 patients who completed a baseline dietary survey, comprised of food records and a food frequency questionnaire (FFQ). Daily energy intake (EI) was adjusted for height and a height-adjusted EI was calculated from the residuals (plus total mean) of a simple regression model of EI on height [13]. Exercise amount (content and frequency) was determined by questionnaire and expressed in kilocalories of energy expenditure per day. Glycohemoglobin A_{1C} assays were standardized with 5.8% as the upper normal limit. All other laboratory tests were determined by standard methods in each clinic. Statistical analyses of male and female data were carried out separately using the SAS software package version 8.0. A p value of less than 0.05 was considered significant.

3. Results

The results, according to quartile of BMI, are shown in Table 1. Despite a 1.4-fold discrepancy in BMI between the highest (BMI-Q4) and the lowest (BMI-Q1) quartiles, no significant linear trend in glycohemoglobin A_{1C} levels between quartiles was seen in either men or women. There was no clear tendency in fasting plasma glucose in BMI-Q2, -Q3 and -Q4, although, it was significantly lower in BMI-Q1. Thus, BMI and glycemic control had only a very modest cross-sectional correlation in these patients. The lack of a significant linear trend in EI, as well as the very minor differences in fat intake and exercise activity between these four categories, indicated that these factors were insufficient to explain the differences in patient BMI. Furthermore, the highest BMI seen in BMI-Q4 was not due to pharmacological treatment because the proportion of patients on insulin therapy was markedly lower than that of the patients in BMI-Q1.

Waist circumference and waist/hip ratio increased in parallel with BMI (Table 1). Blood pressure, total cholesterol and triglycerides increased and HDL cholesterol decreased with the increase in BMI despite the increased frequency of antihypertensive and anti-dyslipidemia medication use, and most of the cardiovascular risk factors that comprise the metabolic syndrome were shown to be significantly elevated with increased BMI.

Quartile analysis according to EI (height-adjusted) (Table 2) revealed a 1.8-fold elevation in EI (i.e. nearly 1000 kcal/day) between the lowest (EI-Q1) and the highest (EI-Q4) quartile, in parallel with a 2-fold increase in fat intake. Nevertheless, the differences in patient BMI between EI-Q1 and -Q4 were no more than 3% (i.e. approximately 2 kg), which supports the previously noted poor correlation between EI and BMI. Furthermore, unlike the BMI categorization (Table 1), there were no significant linear trends in waist size, glycohemoglobin A_{1C}, fasting plasma insulin, blood pressure, serum lipids among the four quartiles, nor any specific trends in exercise activity or pharmacological therapeutic contents (Table 2).

4. Discussion

A common preconception is that patients with higher energy intake are more obese. However, previous population-based studies of mostly non-diabetic subjects revealed a rather inverse correlation between weight and energy intake [13,14], while among European or East Asian patients with established type

Table 1
Baseline characteristics of Japanese patients with type 2 diabetes ($N = 1637$) in the Japan Diabetes Complications Study (JDCS) stratified into quartiles according to their BMI (i.e. BMI-Q1 at lowest and BMI-Q4 at highest)

	Men ($N = 891$)						Women ($N = 746$)					
	Total	BMI-Q1 ($N = 221$)	BMI-Q2 ($N = 223$)	BMI-Q3 ($N = 215$)	BMI-Q4 ($N = 232$)	[a]*P* values	Total	BMI-Q1 ($N = 180$)	BMI-Q2 ($N = 190$)	BMI-Q3 ($N = 189$)	BMI-Q4 ($N = 187$)	[b]*P* values
BMI (kg/m^2)	22.7 (2.6)	19.4 (1.1)	21.7 (0.5)	23.5 (0.5)	26.1 (1.4)		23.3 (3.3)	19.2 (1.3)	22.0 (0.6)	24.1 (0.7)	27.7 (1.9)	
Weight (kg)	62.2 (8.7)	53.0 (5.0)	59.3 (4.5)	64.3 (5.3)	71.7 (6.1)	<0.0001	54.3 (8.5)	44.7 (4.0)	51.8 (3.6)	56.2 (3.9)	64.4 (6.2)	<0.0001
Age (years)	58.4 (7.3)	59.5 (7.0)	59.0 (6.8)	58.1 (7.3)	57.2 (8.0)	0.0003	58.8 (7.3)	58.8 (7.2)	59.4 (7.1)	58.9 (7.0)	58.3 (7.9)	0.4008
Diabetes duration (years)	11.3 (7.4)	12.4 (7.5)	11.9 (7.3)	11.2 (7.6)	9.9 (7.1)	0.0002	10.2 (6.7)	11.6 (7.7)	11.4 (6.8)	9.4 (5.8)	8.6 (5.9)	<0.0001
Waist circumference (cm)	82.1 (7.9)	74.4 (5.8)	79.8 (4.4)	83.6 (5.4)	90.0 (5.9)	<0.0001	76.6 (9.5)	67.6 (6.5)	74.2 (6.7)	78.4 (6.1)	86.2 (7.8)	<0.0001
Waist/hip ratio	0.89 (0.06)	0.85 (0.06)	0.88 (0.05)	0.89 (0.06)	0.93 (0.06)	<0.0001	0.83 (0.07)	0.79 (0.07)	0.83 (0.07)	0.84 (0.06)	0.88 (0.07)	<0.0001
Systolic blood pressure (mmHg)	131 (16)	128 (18)	129 (15)	133 (15)	135 (15)	<0.0001	132 (16)	126 (16)	132 (16)	134 (16)	134 (16)	<0.0001
Diastolic blood pressure (mmHg)	77 (10)	75 (10)	76 (10)	78 (9)	80 (10)	<0.0001	76 (9.9)	73 (9)	75 (10)	78 (9)	78 (10)	<0.0001
Glycohaemoglobin A_{1C} (%)	7.59 (1.33)	7.57 (1.40)	7.70 (1.39)	7.54 (1.30)	7.55 (1.22)	0.6102	8.00 (1.39)	7.89 (1.19)	8.15 (1.53)	7.95 (1.26)	8.02 (1.54)	0.6896
	148	146	153	150	150		155	144	157	157	157	
Fasting plasma glucose[b] (mmol/L)	(130, 178)	(121, 168)	(133, 182)	(130, 175)	(128, 191)	0.0088	(132, 182)	(124, 175)	(133, 182)	(135, 184)	(137, 186)	0.0019
Fasting plasma insulin[c] (pmol/L)[d]	6.0 (0.5, 2.0)	4.3 (0.5, 2.0)	5.0 (0.5, 1.8)	6.2 (0.5, 1.8)	9.2 (0.5, 1.8)	<0.0001	7.0 (0.5, 2.0)	4.7 (0.5, 2.0)	6.5 (0.5, 1.7)	8.5 (0.5, 1.8)	9.0 (0.5, 2.0)	<0.0001
Serum total cholesterol (mmol/L)	193 (35)	184 (34)	194 (32)	201 (37)	194 (34)	0.0004	209 (34)	203 (31)	208 (33)	212 (36)	213 (33)	0.0010
Serum HDL cholesterol (mmol/L)	53 (17)	58 (19)	53 (15)	51 (15)	47 (15)	<0.0001	57 (17)	65 (20)	58 (17)	52 (14)	53 (12)	<0.0001
	109	90	102	116	132		101	78	96	117	119	
Serum triglycerides[c] (mmol/L)	(53, 150)	(57, 140)	(54, 148)	(52, 154)	(54, 147)	<0.0001	(52, 151)	(54, 148)	(54,149)	(53, 152)	(56, 143)	<0.0001
Daily energy intake, height-adjusted (kcal/day)	1817 (45)	1814 (45)	1815 (45)	1817 (49)	1820 (43)	0.1624	1642 (60)	1640 (60)	1649 (56)	1639 (61)	1639 (63)	0.5394
Fat intake (g/day)	54.3 (17.1)	53.4 (16.1)	54.3 (17.9)	55.0 (18.2)	54.7 (16.3)	0.3904	53.2 (18.8)	51.5 (17.1)	51.5 (18.2)	54.3 (19.0)	55.1 (20.5)	0.0278
	163	170	156	179	147		127	113	151	140	125	
Exercise activity[b] (kcal/day)	(55, 354)	(59, 302)	(52, 316)	(64, 393)	(34, 355)	0.0304	(34, 256)	(39, 233)	(50, 259)	(25, 319)	(26, 247)	0.0683
Oral hypoglycaemic reagents; OHA (without insulin) use (%)	60.0	53.4	61.8	61.9	62.9	0.0520[e]	61.0	59.4	65.8	59.3	59.4	0.6558[e]
Insulin (with or without OHA) use (%)	17.2	25.3	17.5	13.5	12.5	0.0002[e]	21.6	27.2	22.6	20.1	16.6	0.0112[e]
Medication for hypertension (%)	23.8	17.9	22.2	28.3	31.6	0.0012[e]	30.5	12.8	20.7	32.6	33.9	<0.0001[e]
Medication for hyperlipidemia (%)	16.4	15.1	19.9	29.4	35.6	<0.0001[e]	33.8	17.9	21.8	32.1	28.2	0.0006[e]

Values are mean (S.D.).
[a] Analysis of variance with contrast test for linear trend.
[b] Median (IQR).
[c] Geometric mean (1 S.D.).
[d] Patients with insulin therapy were excluded.
[e] Mantel test.

Table 2
Baseline characteristics of Japanese patients with type 2 diabetes ($N = 1637$) in the Japan Diabetes Complications Study (JDCS) stratified into quartiles according to their daily energy intake (EI) (height-adjusted) (i.e. EI-Q1 at lowest and EI-Q4 at highest)

	Men ($N = 891$)					Women ($N = 746$)				
	EI-Q1 ($N = 223$)	EI-Q2 ($N = 222$)	EI-Q3 ($N = 224$)	EI-Q4 ($N = 222$)	[a]P values	EI-Q1 ($N = 186$)	EI -Q2 ($N = 187$)	EI -Q3 ($N = 186$)	EI -Q4 ($N = 187$)	[a]P values
Daily energy intake, height-adjusted (kcal/day)	1346 (139)	1658 (73)	1920 (86)	2343 (256)		1199 (160)	1486 (60)	1716 (72)	2165 (339)	
Fat intake (g/day)	37.9 (8.7)	49.0 (10.1)	57.7 (9.9)	72.7 (15.8)	<0.0001	35.7 (8.0)	46.5 (7.9)	55.2 (8.9)	75.0 (19.3)	<0.0001
BMI (kg/m^2)	22.5 (2.5)	22.6 (2.7)	22.7 (2.8)	23.1 (2.5)	0.0165	22.9 (3.4)	23.4 (3.4)	23.0 (3.0)	23.9 (3.2)	0.0234
Weight (kg)	61.7 (8.2)	61.8 (8.6)	61.9 (8.7)	63.4 (9.1)	0.0493	53.8 (8.7)	54.4 (8.6)	53.4 (7.9)	55.9 (8.4)	0.0650
Age (year)	58.0 (7.7)	58.9 (7.4)	58.2 (6.8)	58.6 (7.5)	0.6142	58.8 (7.8)	59.4 (7.6)	59.1 (7.1)	57.9 (6.7)	0.1809
Diabetes duration (year)	11.2 (7.1)	12.1 (7.5)	11.3 (7.3)	10.9 (7.8)	0.4611	10.6 (7.1)	11.2 (7.2)	9.7 (6.4)	9.4 (6.1)	0.0163
Waist circumference (cm)	82.1 (7.3)	81.3 (8.4)	81.7 (7.7)	83.2 (8.0)	0.1039	76.5 (9.0)	76.3 (9.8)	75.6 (9.4)	78.1 (9.8)	0.1905
Waist/hip ratio	0.89 (0.06)	0.89 (0.07)	0.89 (0.06)	0.89 (0.06)	0.6375	0.84 (0.07)	0.83 (0.07)	0.83 (0.07)	0.84 (0.08)	0.8525
Systolic blood pressure (mmHg)	132 (15)	131 (17)	130 (15)	132 (16)	0.8962	131 (17)	133 (16)	131 (16)	132 (16)	0.7616
Diastolic blood pressure (mmHg)	77 (10)	78 (10)	77 (10)	77 (9)	0.7249	75 (10)	75 (10)	77 (10)	77 (10)	0.0548
Glycohaemoglobin A_{1C} (%)	7.59 (1.27)	7.45 (1.24)	7.64 (1.42)	7.67 (1.37)	0.2994	7.85 (1.17)	8.00 (1.35)	8.11 (1.52)	8.05 (1.49)	0.6896
	149	149	149	152		160	156	152	154	
Fasting plasma glucose[b] (mmol/L)	(127, 176)	(127, 180)	(131, 181)	(132, 189)	0.0269	(129, 183)	(134, 187)	(129, 180)	(134, 180)	0.7162
Fasting plasma insulin[c] (pmol/L)[d]	5.7 (0.5, 1.8)	6.5 (0.5, 2.0)	6.0 (0.5, 2.0)	6.0 (0.5, 2.2)	0.6003	6.7 (0.5, 2.0)	7.2 (0.5, 1.8)	6.8 (0.5, 2.0)	7.3 (0.5, 2.0)	0.4112
Serum total cholesterol (mmol/L)	192 (35)	195 (31)	191 (37)	195 (36)	0.6026	210 (35)	211 (33)	207 (34)	208 (32)	0.3835
Serum HDL cholesterol (mmol/L)	51 (16)	54 (18)	53 (16)	52 (16)	0.5414	57 (18)	58 (17)	56(15)	56 (16)	0.3274
	112	110	104	111		97	103	100	105	
Serum triglycerides[c] (mmol/L)	(54, 150)	(55, 145)	(53, 151)	(51, 155)	0.615	(52, 153)	(51,156)	(54, 149)	(53, 150)	0.2595
	138	179	153	160		123	143	133	120	
Exercise activity (kcal/day)	(44, 303)	(67, 363)	(58, 354)	(46, 381)	0.0468	(34, 259)	(49, 289)	(25, 230)	(27, 257)	0.7754
Oral hypoglycaemic reagents (without insulin) use (%)	59.6	62.2	61.6	56.8	0.5327[e]	62.9	62.0	57.0	62.0	0.6333[e]
Insulin (with or without OHA) use (%)	20.2	18.0	14.3	16.2	0.1665[e]	22.0	23.5	23.7	17.1	0.2752[e]
Medication for hypertension (%)	24.2	26.1	21.4	23.4	0.5680[e]	33.3	33.1	28.0	27.3	0.1260[e]
Medication for hyperlipidemia (%)	15.2	18.0	14.7	17.6	0.7513[e]	35.5	35.8	32.3	31.6	0.3381[e]

Values are mean (S.D.).
[a] Analysis of variance with contrast test for linear trend.
[b] Median (IQR).
[c] Geometric mean (1S.D.).
[d] Patients with insulin therapy were excluded.
[e] Extended Mantel test.

2 diabetes, almost no correlation between BMI and non-fasting blood glucose levels was found [15]. Fasting blood glucose, glycohemoglobin, EI and oral medication use were not determined simultaneously in these studies. Our analyses, while revealing that the differences in BMI or EI did not reflect the averaged glycemic control status of patients, also support the earlier studies and provide evidence of relationships between BMI and EI and parameters such as serum lipids and blood pressure. It is also clear from our analyses that it is impossible to ascertain the glycemic control status of an individual patient from a single assessment of their BMI or EI. The lack of significant differences in EI and the relatively small differences in physical activity in the face of a large discrepancy in BMI seen in our patients (Table 1) suggested that lifestyle-related factors play relatively limited roles in determining the current BMI of the patients.

Glycemic control was poorly correlated with BMI while blood pressure and serum lipids showed significant step-wise elevations with increased BMI (Table 1), despite all three parameters reportedly improving with weight loss in intervention studies of diabetic patients [1]. This suggests that the relationship between obesity and hyperglycemia is quite complex. The higher proportion of insulin therapy, and also the longer diabetes duration and the lower fasting plasma insulin levels, seen in patients in the lower BMI categories (Table 1) suggest that Japanese diabetic patients have quite limited insulin secretory capacity and are becoming obese only during the early stages of the disease. This supports previous speculation that the disease process profoundly influences the BMI of patients [4] and could also explain the much lower average BMI in Japanese patients than in white patients [9,10].

Several potential sources of bias need to be considered in interpreting our data. One is BMI-dependent underreporting of energy intake, which has been observed mainly in 24 h dietary recalls [16–18], but also in food frequency questionnaires [18]. However, we combined food recording with FFQ in our dietary survey and observed differences in energy intake (Table 2) that were much broader than the reported BMI-dependent effect (20–25% over the BMI range of approximately 10 kg/m^2) [18]. Another limitation of this study is that we only included patients who had completed a dietary survey for analysis. Neither could we discuss the role of ethnicity because comparable analyses of other ethnic groups could not be found. Such a comparison would have aided our understanding of the underlying pathophysiological relationship between energy intake and obesity in patients with type 2 diabetes and the influence of genetic background on the pathophysiology of the disease.

Acknowledgments

This study was financially supported by the Health Sciences Research Grants (Research on Health Services) provided by the Ministry of Health, Labor and Welfare, Japan. We gratefully acknowledge all the patients, physicians, co-medical staffs and secretaries who are taking part in the JDCS.

Appendix A

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Intima-media thickness of the carotid artery and the distribution of lipoprotein subclasses in men aged 40 to 49 years between whites in the United States and the Japanese in Japan for the ERA JUMP study

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Received 22 May 2007; accepted 17 August 2007

Abstract

In men in the post–World War II birth cohort, that is, men aged 40 to 49 years, whites in the United States had significantly higher levels of intima-media thickness of the carotid arteries (IMT) than the Japanese in Japan (Electron-Beam Tomography and Risk Assessment Among Japanese and US Men in the Post World War II Birth Cohort [ERA JUMP] study). The difference remained after adjusting for traditional risk factors. Primary genetic effects are unlikely, given the degree to which IMT is increased in the Japanese who migrated to the United States. We investigated whether the differences in the distributions of lipoprotein subclasses explain the difference in IMT between the 2 populations. We examined population-based samples of 466 randomly selected men aged 40 to 49 years (215 whites from Allegheny County, Pennsylvania, and 241 Japanese from Kusatsu, Shiga, Japan). Lipoprotein subclasses were determined by nuclear magnetic resonance (NMR) spectroscopy. The whites had significantly higher levels of large very low-density lipoprotein particles and significantly lower levels of large high-density lipoprotein particles than the Japanese, whereas the 2 populations had similar levels of small low-density lipoprotein particles. The 2 populations had similar associations of IMT with NMR lipoproteins. Adjusting for NMR lipoproteins did not attenuate the significant difference in IMT between the 2 populations (0.671 ± 0.006 mm for the whites and 0.618 ± 0.006 mm for the Japanese, $P = .01$, mean ± SE). Differences in the distributions of NMR lipoproteins between the 2 populations did not explain the higher IMT in the whites.

1. Introduction

We have recently reported that among men aged 40 to 49 years, whites in the United States had significantly higher levels of intima-media thickness of the carotid arteries (carotid IMT) than the Japanese in Japan (Electron-Beam Tomography and Risk Assessment Among Japanese and US Men in the Post World War II Birth Cohort [ERA JUMP] study) [1]. The difference remained after adjusting for traditional and other risk factors including fasting insulin, fibrinogen, and C-reactive protein (CRP) [1]. This is despite the fact that levels of total cholesterol and blood pressure have been similar throughout their lifetime between the populations [1]. Moreover, rates of smoking in this birth cohort have been much lower in whites [1]. Primary genetic effects are unlikely, given the degree to which carotid IMT is increased in the Japanese who migrated to the United States [2,3].

Small low-density lipoprotein (LDL) and LDL particle size are associated with carotid IMT independent of total cholesterol or LDL cholesterol (LDL-C) [4-6]. It is possible that levels of small LDL are higher in whites in the United

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doi:10.1016/j.metabol.2007.08.022

States than in the Japanese in Japan, although levels of LDL-C were similar between the 2 populations. No previous study has, however, compared levels of lipoprotein subclasses and their associations with carotid IMT between whites in the United States and the Japanese in Japan.

In this study, we examined whether the difference in the distribution of lipoprotein subclasses between white men in the United States and Japanese men in Japan explains the difference in carotid IMT between the 2 populations.

2. Participants and methods

Detailed descriptions of subjects and methods were published elsewhere except for lipoprotein subclass measurements. Participants were population-based samples of 493 randomly selected men aged 40 to 49 years examined in 2002 to 2005, without clinical cardiovascular disease: 243 white men from Allegheny County, Pennsylvania, and 250 Japanese men from Kusatsu City, Shiga, Japan. In this study, we excluded those taking lipid-lowering medications for the analyses, resulting in 215 whites and 241 Japanese. Informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of University of Pittsburgh, Pittsburgh, PA, and Shiga University of Medical Science, Otsu, Shiga, Japan.

Body weight and height were measured while the participant was wearing light clothing without shoes. Body mass index was calculated as weight divided by the square of the height. Blood pressure was measured with an automated sphygmomanometer (BP-8800; Colin Medical Technology, Komaki, Japan). The average of 2 measurements was used.

Venipuncture was performed early in the clinic visit after a 12-hour fast. The samples were stored at −80C° and shipped on dry ice to the Heinz Laboratory, University of Pittsburgh. Serum lipids were determined using methods standardized by the Centers for Disease Control and Prevention. Serum glucose was determined using an enzymatic assay, serum insulin using a radioimmunoassay (Linco Research, St Charles, MO), CRP using an immunosorbent assay, and fibrinogen using an automated-clot-rate assay (Diagnostica Stago, Parsippany, NJ).

A self-administered questionnaire was used to obtain information on demography, smoking habits, alcohol drinking, and other factors. *Alcohol drinkers* were defined as those who drink alcohol 2 days per week or more. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Diabetes *mellitus* was defined as fasting serum glucose level ≥7 mmol/L (126 mg/dL) or use of antidiabetic medications.

A Toshiba 140A scanner (Toshiba, Tustin, CA and Kawasaki, Japan) equipped with a 7.5-MHz linear array imaging probe was used for carotid scanning at both centers. We used the mean of 8 measurements of the average IMT across 1-cm segments: near and far walls of the common carotid artery (CCA) and the far wall of the carotid bulb and internal carotid artery (ICA) on both sides. The scans were recorded on videotape and sent to the Ultrasound Research Laboratory in Pittsburgh for scoring. We applied continuous quality assessment programs developed by the laboratory to ensure the scanning quality [7], which included standardized protocols, centralized training of technicians, and continuous evaluation of scan quality and protocol adherence by the Ultrasound Research Laboratory. The evaluation of scan quality and protocol adherence was excellent. Under continuous quality assessment programs, correlation coefficients between sonographers and between readers for average IMT were 0.96 and 0.99, respectively [7].

2.1. Lipoprotein subclass measurements

Lipoprotein subclass particle concentrations and average very low-density lipoprotein (VLDL), LDL, and high-density lipoprotein (HDL) particle diameters were determined by nuclear magnetic resonance (NMR) spectroscopy at LipoScience (Raleigh, NC) on serum samples stored at −80C° [8]. Briefly, the NMR method uses the characteristic signals broadcast by lipoprotein subclasses of different size as the basis of their quantification. Particle concentrations of the following lipoprotein species were determined: 3 VLDL subclasses (large, >60 nm; medium, 35-60 nm; and small, 27-35 nm), 3 LDL subclasses (intermediate-density lipoprotein [IDL], 23-27 nm; large, 21.3-23 nm; small, 18.3-21.2 nm), and 3 HDL subclasses (large, 8.8-13 nm; medium, 8.2-8.8 nm; and small, 7.3-8.2 nm) [9]. Weighted average particle sizes of VLDL, LDL, and HDL were calculated from the subclass levels.

2.2. Statistical analyses

To compare risk factors between the populations, a t test for continuous variables except for triglycerides and CRP, the Mann-Whitney U test for triglycerides and CRP, and χ^2 test for categorical variables were used. Spearman correlations of carotid IMT with continuous risk factors were calculated for each population. To compare carotid IMT between the populations, general linear model analyses were performed to calculate multivariate-adjusted carotid IMT. All P values were 2-tailed. P value < .05 was considered as significant. The SPSS software (release 13.0; SPSS, Chicago, IL) was used for all statistical analyses.

3. Results

The whites had lower levels of blood pressure, triglycerides, and glucose and lower rates of cigarette smoking and hypertension than the Japanese. The 2 populations had similar levels of total cholesterol and LDL-C. Meanwhile, the whites were more obese and had higher levels of insulin, fibrinogen, and CRP and lower levels of HDL cholesterol (HDL-C) (Table 1).

The 2 populations had similar levels of small LDL particles. The whites had significantly higher levels of large

Table 1
Characteristics of white men in Allegheny County, Pennsylvania, and Japanese men in Kusatsu, Shiga, Japan, in 2002-2005

	White (n = 215)	Japanese (n = 241)	P
Age (y)	45.0 ± 2.9	45.1 ± 2.8	.64
Body mass index (kg/m^2)	27.5 ± 3.9	23.8 ± 3.1	<.01
Systolic blood pressure (mm Hg)	122.8 ± 11.5	124.8 ± 16.1	.13
Diastolic blood pressure (mm Hg)	73.5 ± 8.8	76.3 ± 11.9	<.01
Total cholesterol (mmol/L)	5.53 ± 0.98	5.64 ± 0.92	.24
LDL-C (mmol/L)	3.54 ± 0.88	3.46 ± 0.92	.33
HDL-C (mmol/L)	1.24 ± 0.33	1.39 ± 0.34	<.01
Triglycerides (mmol/L)	1.38 (1.01, 2.10)	1.53 (1.16, 2.02)	.08
Glucose (mmol/L)	5.53 ± 0.64	5.87 ± 0.87	<.01
Insulin (pmol/L)	100.9 ± 52.4	72.0 ± 31.8	<.01
Fibrinogen (μmol/L)	8.60 ± 2.06	7.38 ± 1.91	<.01
C-reactive protein (mg/L)	0.85 (0.45, 1.83)	0.31 (0.15-0.67)	<.01
Smoker (%)	5.6	49.8	<.01
Drinker (%)	47.0	66.4	<.01
Hypertension (%)	13.5	26.1	<.01
Diabetes (%)	2.3	4.6	.21

Smoker was defined as current smoker; *drinker* as those who drank alcohol ≥2 days a week; *hypertension* as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications; and *diabetes* as fasting glucose level ≥7 mmol/L (126 mg/dL) or use of antidiabetic medications. Values are expressed as mean ± SD or median (interquartile range) for continuous variables.

VLDL, total LDL, and IDL particles. In addition, the whites had significantly lower levels of total, large, and medium HDL particles (Table 2).

Table 2
Comparison of lipoprotein subclasses among men aged 40 to 49 years between whites in Allegheny County, Pennsylvania, and the Japanese in Kusatsu, Shiga, Japan, in 2002-2005

	Whites (n = 215)	Japanese (n = 241)	P
Lipoprotein particle concentration			
VLDL particles (nmol/L)			
Total	91.7 ± 43.5	91.8 ± 45.2	.80
Large	1.46 (0.59, 6.22)	0.50 (0.10, 2.75)	<.01
Medium	34.1 (17.5, 55.5)	40.3 (18.7, 58.8)	.14
Small	46.3 ± 21.3	44.0 ± 24.7	.28
LDL particles (nmol/L)			
Total	1491.9 ± 415.8	1410.6 ± 443.1	<.05
IDL	40.8 (10.2, 80.3)	18.0 (0.0, 53.5)	<.01
Large	524.9 ± 283.8	514.8 ± 224.1	.67
Small	915.1 ± 523.9	861.6 ± 511.1	.27
HDL particles (μmol/L)			
Total	31.5 ± 5.7	35.0 ± 6.1	<.01
Large	5.2 ± 3.2	8.4 ± 3.8	<.01
Medium	0.06 (0.00, 1.22)	1.10 (0.00, 3.30)	<.01
Small	25.2 ± 25.2	23.9 ± 23.9	<.01
Lipoprotein particle size (nm)			
VLDL	49.6 ± 7.9	44.0 ± 7.0	<.01
LDL	20.9 ± 0.9	21.1 ± 0.8	.15
HDL	8.6 ± 0.5	9.1 ± 0.4	<.01

Values are expressed as mean ± SD or median (interquartile range) for continuous variables.

The 2 populations had similar associations of carotid IMT with NMR lipoproteins. Both populations had positive associations of carotid IMT with total LDL, IDL, and small LDL particles and negative associations of carotid IMT with LDL size, large HDL particles, and HDL size. Although only the whites had significant associations of carotid IMT with large VLDL particles and VLDL size (Table 3), there was no significant interaction between the 2 populations and each of the VLDL particle and VLDL size in predicting carotid IMT. Similarly, although only the whites had significant associations of carotid IMT with total cholesterol and triglycerides and only the Japanese had a significant association of carotid IMT with HDL-C (Table 3), there was no significant interaction between the 2 populations and each of total cholesterol, triglycerides, and HDL-C in predicting carotid IMT.

Generally, the whites had significant associations of carotid IMT with NMR lipoproteins independent of standard lipids. The associations with total LDL, small LDL particles, and LDL size were independent of LDL-C (P = .01, .02, and .02, respectively). The associations with large HDL and HDL size were independent of HDL-C (P = .01 and <.01, respectively). Meanwhile the associations with large VLDL particles and VLDL size were not independent of triglycer-

Table 3
Spearman correlations of lipoprotein subclasses with carotid IMT among white men aged 40 to 49 years in Allegheny County, Pennsylvania, and among Japanese men aged 40 to 49 years in Kusatsu, Shiga, Japan, in 2002-2005

	Whites (n = 215)		Japanese (n = 241)	
	ρ	P	ρ	P
Lipoprotein subclasses				
Lipoprotein particle concentration				
VLDL particles				
Total	0.08	.23	−0.03	.61
Large	0.13	.05	0.01	.78
Medium	0.03	.72	−0.05	.48
Small	0.08	.25	0.01	.83
LDL particles				
Total	0.24	<.01	0.12	.06
IDL	0.12	.09	0.11	.08
Large	0.00	.95	−0.06	.37
Small	0.19	.01	0.12	.05
HDL particles				
Total	−0.01	.86	−0.09	.16
Large	−0.18	.01	−0.16	.01
Medium	−0.02	.74	0.03	.68
Small	0.06	.37	0.05	.42
Lipoprotein particle size				
VLDL	0.13	.06	−0.03	.68
LDL	−0.13	.06	−0.12	.07
HDL	−0.19	.01	−0.14	.03
Standard lipids				
Total cholesterol	0.23	<.01	0.09	.16
LDL-C	0.22	<.01	0.13	.04
HDL-C	−0.09	.21	−0.19	<.01
Triglycerides	0.14	.04	0.03	.65

Table 4
Comparison of multivariate-adjusted carotid IMT (in millimeters) among men aged 40 to 49 years between whites in Allegheny County, Pennsylvania, and the Japanese in Kusatsu, Shiga, Japan, in 2002-2005

	Whites (n = 215)	Japanese (n = 241)	P
Model I	0.676 ± 0.006	0.613 ± 0.006	<.01
Model II	0.671 ± 0.006	0.618 ± 0.006	<.01
Model III	0.666 ± 0.007	0.622 ± 0.006	<.01
Model IV	0.666 ± 0.007	0.622 ± 0.006	<.01

Model I: adjusted for age, systolic blood pressure, and current smoking; model II: further adjusted for large VLDL, total LDL, and large HDL particles; model III: further adjusted for BMI, glucose, and insulin; model IV: further adjusted for fibrinogen, CRP, and alcohol. Values are expressed as mean ± SE.

ides. In contrast, the Japanese did not have significant associations of carotid IMT with NMR lipoproteins independent of standard lipids.

The whites had a significantly higher carotid IMT than the Japanese after adjusting for age, blood pressure, and current smoking; the difference remained after further adjusting for NMR lipoproteins (model II in Table 4). The significant difference remained after further adjusting for other factors (models III and IV in Table 4). Further adjusting for standard lipids did not change the result.

4. Discussion

This population-based study in men aged 40 to 49 years has shown that whites in the United States had significantly higher large VLDL particles and significantly lower large HDL particles than the Japanese in Japan and that the difference in the lipoprotein distribution between the 2 populations did not explain the difference in carotid IMT. In addition, the study has shown that the associations of NMR lipoproteins with carotid IMT were similar between the 2 populations and that the distributions of LDL particles were similar between the 2 populations. This is the first population-based study comparing the association of carotid IMT with NMR lipoproteins between whites in the United States and the Japanese in Japan.

Carotid IMT is considered to be a surrogate marker of generalized atherosclerosis [10]. Increased carotid IMT and its progression are associated with cardiovascular risk factors in Americans and the Japanese [11-14]. Carotid IMT is an independent risk factor for cardiovascular disease in Americans and the Japanese [15,16].

Reported ethnic differences in carotid IMT are congruent with ethnic differences in mortality from coronary heart disease (CHD) [17-19], which is consistent with the result of our study and CHD mortality statistics [20]. No previous study has, however, examined whether the ethnic difference in the distribution of lipoprotein subclasses explains the ethnic difference in carotid IMT. Some studies showed that the ethnic difference in IMT of ICA but not CCA becomes insignificant after adjusting for risk factors [17,19]. In our study, however, the significant differences in both ICA and CCA remained after adjusting for NMR lipoproteins (data not shown).

Differences in genetic factors or lifetime exposures to traditional risk factors do not appear to explain the difference in carotid IMT. As for genetic factors, a study of Japanese migrants to the United States showed that Japanese Americans had significantly greater carotid IMT than the Japanese in Japan [2,3]. Japanese Americans appear to have greater carotid IMT than whites in the United States in the same age group [21]. As to lifetime exposure to traditional risk factors, available data from national or population-based surveys in this birth cohort, that is, those aged 40 to 49 years, show that white men in the United States and Japanese men in Japan have had very similar levels of total cholesterol and blood pressure from childhood [22-25] to adulthood [26,27]. Furthermore, white men have had much lower rates of cigarette smoking than Japanese men [26,27].

Other potential explanations may be differences in levels of insulin resistance and fish consumption. Insulin resistance is associated with carotid IMT in both whites and the Japanese independent of traditional risk factors [28,29]. Because the whites were significantly more obese than the Japanese, the whites are expected to be more insulin resistant. Significantly higher large VLDL and lower large HDL particles in whites than in the Japanese support this hypothesis [30]. Although we adjusted for fasting insulin, levels of fasting insulin alone do not necessarily represent insulin resistance [31]. The difference in prevalence of metabolic syndrome by the criteria of the International Diabetes Federation [32] did not explain the difference in IMT between the 2 populations either (data not shown). A cross-sectional study in Japan reported that fish consumption is significantly and inversely associated with carotid IMT [33]. Because whites in the United States eat much less fish than the Japanese [26], this may be associated with higher carotid IMT in the whites. Further investigations are needed.

Our observation that the whites had a significant association of carotid IMT with small LDL independent of LDL-C is in accordance with previous reports [4-6]. In addition, we found that the whites had significant associations of carotid IMT with large HDL particles independent of HDL-C. The reasons why we did not observe these independent associations in the Japanese remain unexplained.

The study has several limitations. The study is cross-sectional in design, and we cannot establish any causality. The study examined men aged 40 to 49 years only. We focused on this specific sex and age group because population levels of total cholesterol and blood pressure have been similar between the Japanese and whites throughout their lifetime. Levels of total cholesterol have been higher in whites than the Japanese in older age groups. A profile of traditional risk factors in women has been less favorable in US whites than in the Japanese [1]. The fact that the population levels of total cholesterol and blood pressure have been similar throughout their lifetime does not

necessarily mean that the men in these 2 populations had similar trajectory of these risk factors. Based on CHD mortality statistics in men aged 35 to 44 years in examined areas, however, populations examined in this study are unlikely to deviate largely from nation-representing samples [34,35]. Based on the rate of cigarette smoking, the whites in this study may be healthier than the general white population. This does not, however, change our results that the whites had higher carotid IMT than the Japanese. Although there was no interaction between populations and each of the NMR lipoproteins and standard lipids in predicting the IMT, this may be due to the small sample size. Although we excluded those without lipid-lowering medications, the conclusion remains the same when we included all participants.

In conclusion, the study shows that in men aged 40 to 49 years, whites in the United States had significantly higher VLDL particles and significantly lower HDL particles than the Japanese in Japan; but the differences in the lipoprotein distributions between whites in the United States and the Japanese in Japan did not explain the higher carotid IMT in the whites.

Acknowledgment

This research was supported by grants R01 HL68200 from the National Institutes of Health and B 16790335 and A 13307016 from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

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Review

Explanation for the Japanese Paradox: Prevention of Increase in Coronary Heart Disease and Reduction in Stroke

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Japan's age-adjusted rate for mortality from stroke increased after the Second World War until 1965 and then showed a significant decline until 1990; however, the age-adjusted rate for mortality from all heart disease and coronary heart disease (CHD) increased until 1970 and then declined slowly. A puzzling question is why the rate of mortality from CHD declined in spite of an increase in serum total cholesterol level following an increase in fat consumption.

It was confirmed that CHD incidence was far lower in several Japanese populations compared to Western countries in the "Monitoring Trends and Determinants in Cardiovascular Disease" (MONICA) project; therefore, the lower CHD mortality in Japan stems from the lower CHD incidence. CHD risk factors based on epidemiologic cohort studies in Japan were no different from those of other industrialized countries: hypertension, hypercholesterolemia, smoking and diabetes mellitus (DM). So, how can we explain this phenomenon?

There are three possible explanations. One is the decline in population blood pressure level and the prevalence of hypertension during the years 1965-1990; the second is the decline in smoking rate in men and women; the third is that the serum total cholesterol level for middle-aged and elderly populations remains 5-15 mg/dL lower than that of the US elderly counterpart, although men aged 40-49 in Japan and the US had similar serum total cholesterol levels. It was also noted that elderly people in Japan, as observed in the Seven Countries Study, had far lower serum total cholesterol levels in midlife, i.e., around 160 mg/dL in the 1960s. This was not the case for elderly in the US where a higher serum total cholesterol level was observed in midlife.

In conclusion, the lower serum cholesterol level in the past of Japanese middle-aged and elderly people compared to Western counterparts helps to maintain the low CHD incidence and mortality supported by the declining trend in blood pressure level and smoking rate for both men and women.

J Atheroscler Thromb, 2007; 14:278-286.

Key words; Coronary heart disease, Epidemiology, Serum total cholesterol, Hypertension, Blood pressure, Smoking rate, Diabetes mellitus

Introduction

The high life expectancy rate in Japan has led the world for over 20 years[1]. This position has been maintained since the mid-1980s by overcoming the highest stroke mortality rate in the world and also preventing an increase in coronary heart disease (CHD)[2-5]. The question raised is why Japanese people have lower CHD mortality and incidence than other industrialized countries in spite of an increase in serum total cholesterol following an increase in fat consumption and a high smoking rate[6].

This review article discusses the possible reasons for this phenomenon after reviewing trends in stroke and CHD mortality, and associated risk factors.

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Received: June 25, 2007
Accepted for publication: July 7, 2007

Trends in Stroke and Heart Disease Mortality

Age-adjusted all-stroke mortality in Japan increased after the Second World War until 1965 and then

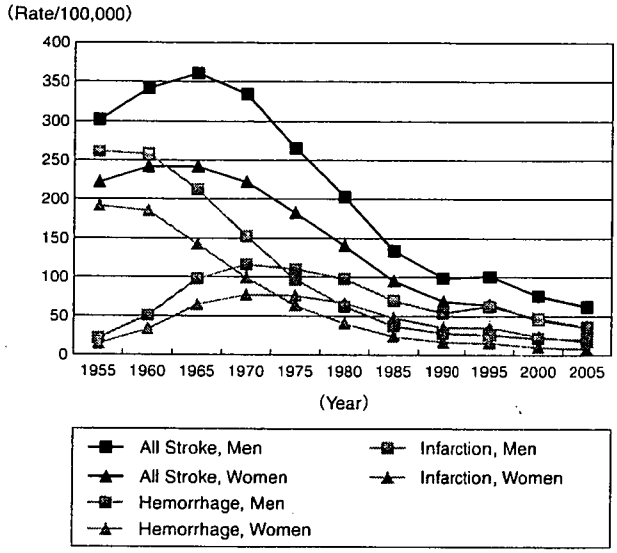


Fig. 1. Change in age-adjusted stroke mortality in Japan by gender.

Age-adjusted all-stroke mortality for men and women peaked in 1965 and then declined substantially until 1990. Cerebral hemorrhage was higher than cerebral infarction when all-stroke mortality was highest. Although cerebral infarction showed a peak in 1970, this was later than that of all-stroke mortality, and it declined thereafter. Age-adjusted all-stroke mortality has slowed down since around 1990.

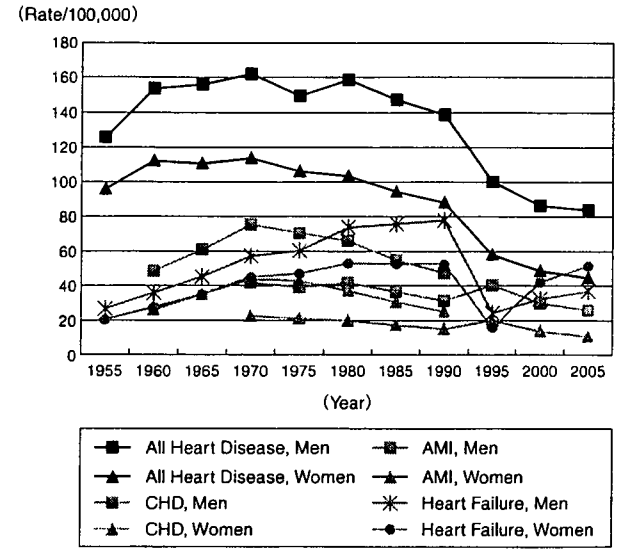


Fig. 2. Change in age-adjusted heart disease mortality in Japan by gender.

Age-adjusted all heart disease and coronary heart disease mortality peaked around 1970, 5 years later than that of all-stroke mortality. This has also declined steadily. The sudden change in mortality from the all heart disease and heart failure before and after 1995 was due to the change in the diagnostic approach for heart failure. Age-adjusted mortality from acute myocardial infarction maintained a low rate with a slightly downward trend. A slight increase in 1995 for acute myocardial infarction was also due to the diagnostic change.

showed a significant decline until 1990 (**Fig. 1**)[4]. In fact, an approximately 80% reduction in age-adjusted all stroke mortality occurred during 1965-1990. On the other hand, age-adjusted mortality from all heart disease and CHD increased until 1970 and then gradually declined (**Fig. 2**)[2-6]. Even in 1970, age-adjusted mortality from all heart disease, CHD and acute myocardial infarction (AMI) was far lower than that of stroke (**Fig. 2**)[2-4]. Age-adjusted all-stroke mortality in 1965 in Japan was recorded as the highest rate in the world[2, 4] whereas age-adjusted CHD and/or AMI mortality around 1970 was one of the lowest rates among industrialized countries, as in some Mediterranean countries[5].

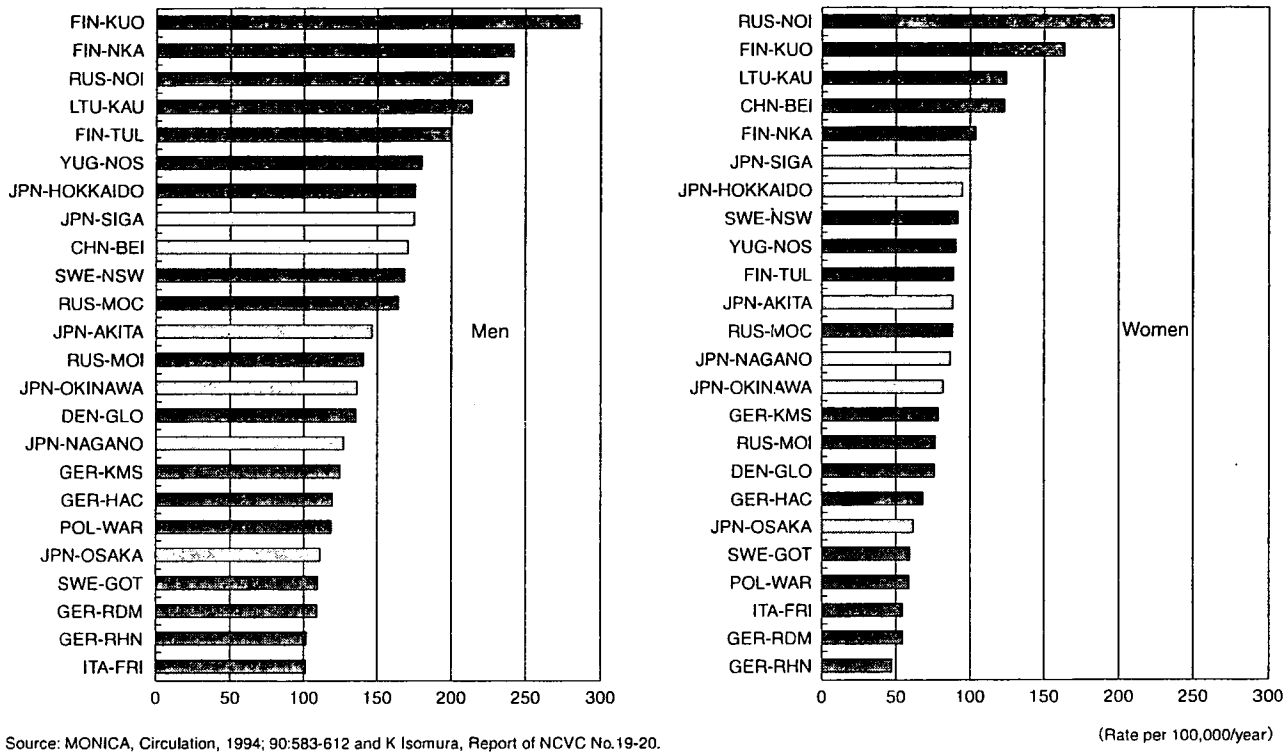
The high stroke rate and low CHD mortality rate is a specific feature of Japan among industrialized countries and it continues to the present day, although we were able to greatly reduce stroke mortality during 1965-2000.

A number of arguments remain regarding the diagnostic approach in Japan's lower CHD mortality compared to other industrialized countries, because the diagnosis of heart failure has a higher proportion in Japan than in the US[6]; however, even if heart failure is combined with mortality from ischemic heart disease, the rate is still lower in Japan than in the US[6]. In addition, mortality from all heart disease is also lower[6].

Validation studies on the incidence rate of myocardial infarction were carried out in Osaka and Kyushu[7, 8]. The two studies examined the extent to which heart failure should be classified as AMI, and concluded that the myocardial infarction rate did not change significantly due to misclassification of heart failure[7, 8]. Some incidences of heart failure should be classified as myocardial infarction, while some incidences of myocardial infarction should be excluded. Therefore, mortality from all heart disease as well as from CHD was lower in Japan than in the US and other Western countries.

Trends in Incidence of Stroke and Myocardial Infarction

The incidence of stroke, either thrombotic or hemorrhagic, has declined in accordance with stroke mortality[9-15]. Epidemiologic studies reveal that more than half the decline in stroke mortality can be explained by the decline in its incidence[9-15]. It is also



Source: MONICA, Circulation, 1994; 90:583-612 and K Isomura, Report of NCVC No.19-20.

Fig. 3. Age-adjusted (35-64 years) stroke incidence for MONICA and a Japanese study.

Age-adjusted (35-64 years) stroke incidence was compared between the MONICA study in 1985-87 and a Japanese study in 1989-92. The diagnostic criteria of the MONICA study were used for the Japanese study. Stroke incidence for the six Japanese populations showed that the rate was in the middle of these populations and definitely lower than that of Finland.

true that the decline in CHD mortality since 1970 brought about the decline in the incidence of acute myocardial infarction[9-16].

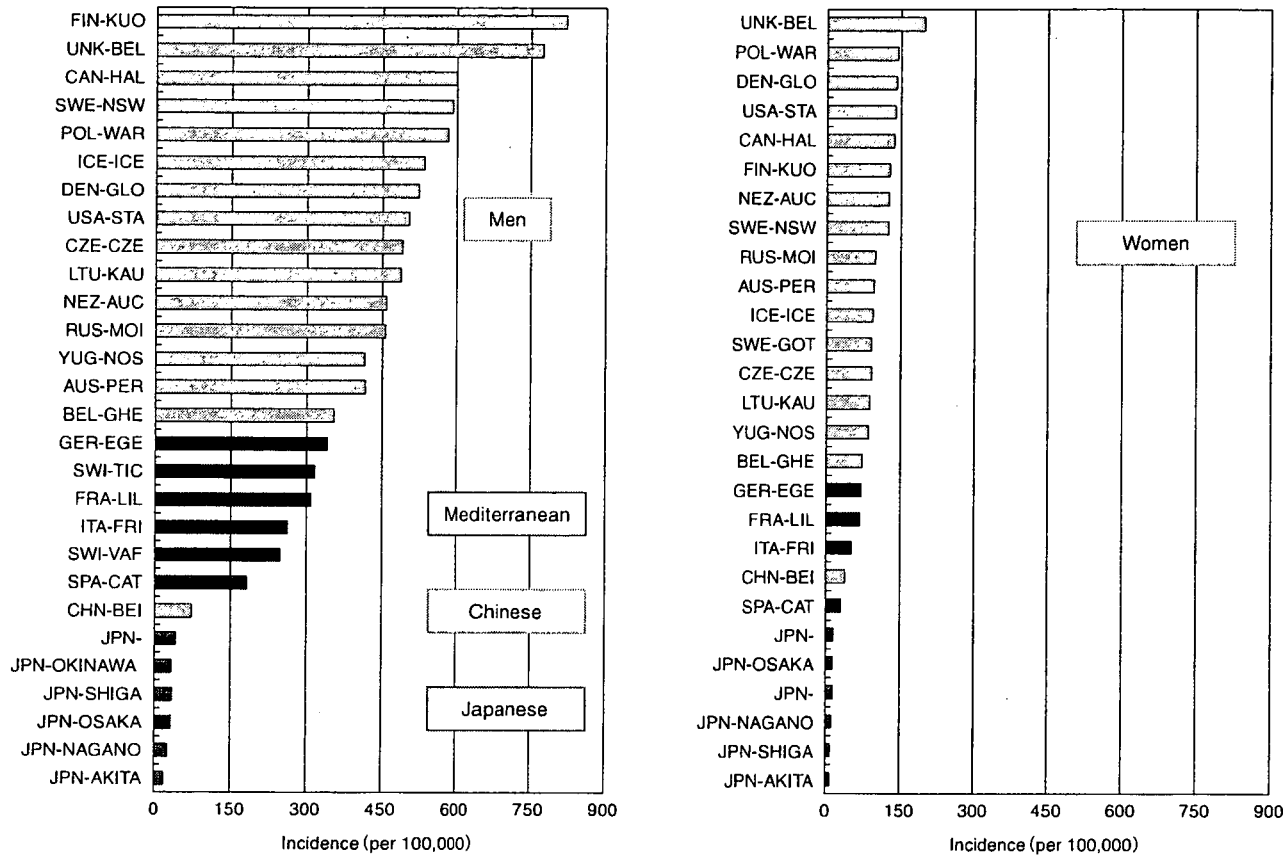
The Hisayama Study compares the incidence of CHD as well as AMI, asymptomatic myocardial infarction and sudden death among three cohorts; the oldest is a survey taken during 1961-73, the second one during 1974-1986, and the latest during 1988-2000[10]. Since the Hisayama Study is a long-term cohort study with around 80% autopsy cases, it is suitable for determining trends in CHD[9, 10]. The trend in CHD incidence in the Hisayama Study showed a decline between the second cohort and the third latest cohort, which is compatible with the trend in CHD mortality in Japan. The Hiroshima/Nagasaki Study also found that the trend in incidence of AMI was similar to that in CHD mortality in Japan[13].

International Comparison of the Incidence of Stroke and Myocardial Infarction

Six Japanese cohorts are available for comparing the incidence of AMI with that of the MONICA Project (multinational monitoring of trends and determinants in cardiovascular disease) conducted by WHO[15-18]. The MONICA Project started monitoring trends in AMI and stroke incidence, and their risk factors in 1985[19, 20]. Shortly afterwards, six Japanese cohort studies were conducted using the same registration criteria for stroke and AMI, making it possible to compare data with that of the MONICA Project[15-20] (**Fig. 3, 4**).

For stroke incidence, six Japanese populations were included among the MONICA populations. The data show that the Japanese populations did not have a higher incidence rate of stroke compared to MONICA populations in the world; in fact, the Osaka population had a considerably lower incidence of stroke. These results are compatible with those of stroke mortality world statistics, as shown in **Fig. 1**.

As for AMI, all six Japanese populations showed the lowest incidence rates among these populations (**Fig. 4**). The incidence in Finnish and British populations for men was 10 to 15 times higher than that



Circulation, 1994; 90:583-612 and K Isomura, Report of NCVC No.19-20.

Fig. 4. Age-adjusted (35-64 years) incidence of acute myocardial infarction in MONICA and a Japanese study.

Age-adjusted (35-64 years) incidence of acute myocardial infarction was compared between the MONICA study in 1985-87 and a Japanese study in 1989-92. The diagnostic criteria of the MONICA study were used for the Japanese study. The incidence of acute myocardial infarction in six Japanese populations was far lower than that in other MONICA populations followed by China and Mediterranean countries' populations.

of Japanese populations. China and Mediterranean countries were also lower than other countries but higher than Japanese populations. This incidence pattern is also similar to that of CHD mortality in the world[1-5, 15-20]; therefore, the lower CHD mortality in Japan stems from the lower CHD incidence compared to other industrialized countries.

Risk Factors for Stroke and CHD in Japan

The most potent risk factor for stroke, either cerebral hemorrhagic or infarction, is high blood pressure[21-25], although hypertension is more specific to cerebral hemorrhage than to cerebral infarction. The higher the blood pressure, the higher the risk ratio. There is no threshold between blood pressure and stroke occurrence[22-24] and this holds true for the young and old[23].

Smoking was not found to be a risk factor for stroke in the past[26, 27]; however, recent large cohort studies in Japan, i.e. NIPPON DATA80, show a clear graded relationship between smoking and stroke[28-30], as has been found in Western countries[31, 32]. One explanation is that the magnitude of hypertension as a strong risk factor weakened due to the decline in population blood pressure level[3-5]. Since the smoking rate for Japanese men is around 50% in spite of a substantial decline, the population smoking risk contributable to stroke in men is around 30%; this means that 30% of strokes in men would be prevented by smoking cessation[21]. In addition, it is estimated based on Japanese cohort studies that a 1% reduction in the smoking