

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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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 \pm SE). Differences in the distributions of NMR lipoproteins between the 2 populations did not explain the higher IMT in the whites. © 2008 Elsevier Inc. All rights reserved.

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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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 -80°C 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 -80°C [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
<i>Lipoprotein subclasses</i>				
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
<i>Standard lipids</i>				
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.

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