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Higher liver fat content among Japanese in Japan compared with non-Hispanic whites in the United States

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Abstract

Among Asians, including Japanese, obesity is related to dyslipidemia and insulin resistance at a lower level of body mass index (BMI) compared with non-Hispanic whites (NHW). We hypothesize that this ethnic difference in the relationship between BMI and metabolic risks is partly associated with the ethnic difference in fat distribution, namely, liver fat as well as visceral adipose tissue. To compare liver fat content among Japanese vs NHW men, regional computed tomographic images were taken to measure liver computed tomographic density in population-based samples of 313 Japanese and 288 NHW men aged 40 to 49 years, along with the assessment of metabolic parameters. Liver fat content was higher in Japanese than NHW men (liver to spleen attenuation ratio [lower value means higher liver fat content]: 1.01 ± 0.16 vs 1.07 ± 0.15, respectively; $P < .01$), despite a lower mean BMI in Japanese men (BMI: 23.6 ± 2.9 vs 27.8 ± 4.2 kg/m^2, $P < .01$). Moreover, Japanese men had a greater disposition for fatty liver with a small increase in BMI than NHW ($P < .01$), whereas both groups had a similar relationship between visceral adipose tissue and BMI. In both groups, liver fat content correlated with triglycerides, homeostasis model assessment of insulin resistance, and C-reactive protein. Liver fat content is higher among Japanese than NHW; and this ethnic difference becomes more robust with a small increase in BMI, suggesting that fatty liver is a sensitive marker for the failure of the adipose tissue to expand to accommodate an increased energy influx, and is associated with similar metabolic risk in Japanese despite lower BMI compared with NHW men.

1. Introduction

Obesity is a risk factor for dyslipidemia and insulin resistance (IR). In clinical practice and large epidemiologic studies, overweight and obesity status is measured by the use of body mass index (BMI) [1]. Body mass index correlates with fat mass (FM), although there can be a substantial interindividual variation in the percentage of weight accounted for by FM within the BMI range designated as overweight [2].

Moreover, the "dose-response" relationship between BMI and metabolic risk, that is, dyslipidemia and IR, appears to differ with ethnicity. Among many Asian groups, lower BMI is related to greater metabolic risks when compared with

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non-Hispanic whites (NHW) [3,4]. The reasons for the ethnic differences in the relationship between BMI and metabolic risk are uncertain. Some data, however, suggest that Asians compared with NHW have a higher percentage of body fat within the "overweight" BMI categories [5,6] and that patterns of adipose tissue (AT) distribution differ.

Visceral adipose tissue (VAT) is associated with IR and dyslipidemia [7-12]. Ethnic differences in VAT have been noted. A recent meta-analysis has shown that Japanese adults have a propensity for greater VAT [3,13] than subcutaneous adipose tissue (SAT) [14]. We have recently reported that Japanese men have greater VAT compared with NHW after adjusting for differences in waist girth [15]. In addition, Asian Indians also have greater VAT after adjusting for BMI, compared with NHW [16].

Fatty liver has been shown to be associated with VAT, dyslipidemia, and IR [17-21]. Ethnic differences in the prevalence of fatty liver have been noted between African Americans and NHW [22,23]. Very few studies, however, have reported ethnic differences in fatty liver between Asians and NHW [23].

Prior studies have shown a strong negative correlation between computed tomographic (CT) density in the liver and fatty infiltration measured by biopsy [24,25], wherein lower values for CT density denote higher lipid content in the liver. The ratio of liver to spleen (L/S ratio) for CT attenuation value is another index, with an L/S ratio less than 1 considered to represent fatty liver [24-26].

We hypothesize that liver fat is greater in Japanese men in Japan than in NHW men in the United States, and this is associated with comparable metabolic risks in Japanese men despite a lower BMI [27]. To test this hypothesis, we compared liver fat content evaluated using CT imaging of the liver and the spleen (L/S ratio) between population-based samples of 313 Japanese and 288 NHW men aged 40 to 49 years (**E**BCT and **R**isk Factor **A**ssessment among **J**apanese and **U**.S. **M**en in the **P**ost World War II Birth Cohort [ERA JUMP] Study) [27]. We also explored the association of liver fat content with metabolic parameters such as triglyceride (TG) level.

2. Methods

2.1. Subjects

The research design and methods of the ERA JUMP Study have been described previously [27]. Briefly, we examined population-based samples of 623 men aged 40 to 49 years without clinical cardiovascular disease, type 1 diabetes mellitus, or other severe conditions from 2002 to 2006: 313 Japanese men in Kusatsu City, Shiga, Japan, and 310 NHW men living in Allegheny County, Pennsylvania. Among 310 NHW men, CT images were available only for 288 subjects. The study was approved by the Institutional Review Boards of Shiga University Medical Science, Otsu, Japan, and the University of Pittsburgh, Pittsburgh, PA.

2.2. Metabolic risk factors

Height and weight were measured on calibrated scales. Adiposity was estimated using BMI, which is calculated as weight (in kilograms)/height (in meters)^2. Waist girth (in centimeters) was measured at the level of the umbilicus while the participant was standing erect.

Venipuncture was performed early in the clinic visit after a 12-hour fast. Serum samples were analyzed at the Heinz Laboratory, Department of Epidemiology, University of Pittsburgh, as described previously [27]. Briefly, lipid levels were determined using the standardized methods of the Centers for Disease Control and Prevention, including total cholesterol, high-density lipoprotein cholesterol, and TG. Fasting serum glucose was determined by an enzymatic procedure; and fasting insulin, by radioimmunoassay (Linco Research, St Charles, MO). Homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin sensitivity: HOMA-IR = glucose (in milligrams per deciliter) $*$ insulin (in microunits per milliliter)/405 [28]. Plasma samples were analyzed at the Laboratory for Clinical Biochemistry Research, University of Vermont. High-sensitivity C-reactive protein (CRP) was determined by a colorimetric competitive enzyme-linked immunosorbent assay.

A self-administered questionnaire was used to obtain current medication use, habitual alcohol intake (yes = 1, no = 0), and demographic information such as dietary habits. Alcohol intake was assessed as whether the participant drank beer, wine, liquor, sake (Japanese rice wine), or other alcoholic beverages, with quantity and frequency recorded. Ethanol consumption per day was estimated, assuming that concentrations of alcohol were 5% for beer, 12% for wine, 40% for liquor, and 16% for sake. *Habitual alcohol intake* was defined as drinking 2 times per week or more.

2.3. Body composition by CT imaging

Computed tomographic images were taken to measure liver CT density. Scanning was performed using a GE-Imatron C150 Electron Beam Tomography scanner (GE Medical Systems, South San Francisco, CA) at both study sites. Images centered on the T12-L1 disc space and the L4-5 disc space were used for assessing hepatic fat content and abdominal AT distribution, respectively. Computed tomographic imaging provides information on spatial arrangement of tissues, with the contrast between tissues based upon differences in attenuation of energy from radiographs. Attenuation values for CT are expressed using water as a reference value of 0 Hounsfield unit (HU). Adipose tissue displays attenuation values that are negative to those of water and in a range from −190 to −30 HU, whereas skeletal muscle values are in a range from 0 to 100 HU [29]. The amount of fat deposition within the liver can also be characterized on the basis of its effect upon CT attenuation values of the liver. Prior studies have shown a strong negative correlation between CT density in the liver and fatty infiltration measured by biopsy [24,25], wherein lower values for CT density denote higher lipid content in liver. In the current study, to assess hepatic fat content, CT attenuation in HU was determined in 3 regions of interest (ROIs) for the liver and the spleen, with each ROI approximately 120 mm^2. The ROI for the liver was placed manually to avoid major vessels. By using the ratio of liver to spleen attenuation, that is, using spleen as an internal control, possible confounding factors across images such as the effect of obesity are reduced. Higher BMI is associated with lower CT attenuation [30,31]; and therefore, L/S ratio is used as an index of liver fat content [24-26]. On the CT images of the abdomen, the area for AT and the psoas muscles was measured electronically by defining for each tissue a range of CT attenuation values: −30 to −190 HU for AT and 0 to 100 HU for muscle, as previously described [18]. To determine the respective areas of VAT and SAT, a separation line was drawn manually using a cursor along the abdominal wall musculature in continuity with fascia of the paraspinal muscles. Again, these measurements were performed by a cross-sectional image at L4-5 and were estimates for AT volume (distribution) [32,33]. All CT images were analyzed at the University of Pittsburgh using image analysis software by 1 trained reader (SliceOmatic; Tomovision, Montreal, Canada).

2.4. Statistical analysis

Statistical analyses were performed using SPSS 14.0 (SPSS, Chicago, IL). General linear models were used to examine ethnic differences in body composition and metabolic parameters and to assess the association of liver CT density with selected parameters. Two-way analysis of variance was also used to assess the BMI × ethnicity interaction for liver fat, and BMI was used as a continuous variable. However, the data were presented in categories for ease of visualization. The L/S ratio was also presented as categorized despite being using as a continuous variable, and analysis of covariance was used to assess the ethnic difference. A P value less than .05 was considered statistically significant. All tests were based on a 2-sided level of significance.

3. Results

3.1. Body composition

Clinical characteristics and body composition parameters for Japanese and NHW men are presented in Table 1 (unadjusted values). By design, the 2 groups were very similar for age. Japanese men were shorter (170 ± 6 vs 180 ± 7 cm, $P < .01$) and lighter, by about 4 BMI units, than NHW men ($P < .01$). Japanese men had significantly smaller waist girth than NHW men (85 ± 8 vs 99 ± 12 cm, respectively; $P < .01$). Japanese men had significantly smaller VAT by 25% and SAT by 80% (Table 1). The ratio of VAT to SAT was higher in Japanese men, suggesting a greater disposition for storing fat calories in VAT relative to SAT among Japanese compared with NHW men. In support of this postulate, group comparisons for VAT were conducted; and —after adjusting for the effects of BMI and waist circumference—the results indicated a 7 ± 3-cm^2 greater VAT in the Japanese compared with NHW men ($P < .01$).

Also shown in Table 1 are unadjusted mean values for liver attenuation, spleen attenuation, and the L/S ratio. The L/S attenuation ratio was significantly lower in Japanese men, meaning greater liver fat content among Japanese compared with NHW men; mean liver CT attenuation was similar across groups, although spleen CT attenuation was significantly higher in Japanese men. To investigate this finding, we explored the relationship between spleen CT attenuation and abdominal SAT. Higher amounts of SAT correlated with lower spleen CT attenuation ($P < .01$). After adjustment for SAT, there was no significant group difference in spleen CT attenuation. This lends support to the methodological value of presenting data on liver CT attenuation as the L/S attenuation ratio, using the spleen attenuation as an internal control [25] for volume-averaging effects related to abdominal SAT. The percentage of men with a low value for the L/S ratio (ie, <1) that is recognized to be consistent with fatty liver as determined at biopsy [24,25] was significantly higher in Japanese men (33.1% vs 24.7%, $P < .05$). This further supports that Japanese men had higher liver fat content than NHW men.

The L/S ratio did not correlate with habitual alcohol intake or daily ethanol intake in this study, analyzing the 2

Table 1
Basic clinical characteristics and body composition assessed by CT in Japanese in Kusatsu City, Shiga, Japan and NHW men in Allegheny County, Pennsylvania, aged 40 to 49 years in 2002-2005

	Japanese men (n = 314)	NHW men (n = 288)
Age (y)	45.1 ± 2.8	45.0 ± 2.8
Weight (kg)	68.6 ± 9.6	90.3 ± 14.9*
BMI (kg/m^2)	23.6 ± 2.9	27.8 ± 4.2*
Alcohol intake (g/d)	27 ± 29	10 ± 14*
Metabolic parameters		
TG (mg/dL)	155 ± 81	152 ± 100
HOMA-IR	2.77 ± 1.51	3.89 ± 2.76*
Prevalence of diabetes (%)	6.1%	3.1%
CRP (mg/dL)	0.74 ± 1.79	1.62 ± 2.36*
CT imaging of the abdomen		
VAT (cm^2)	80 ± 30	103 ± 44*
SAT (cm^2)	82 ± 35	151 ± 67*
VAT/SAT ratio	1.05 ± 0.33	0.74 ± 0.28*
Abdominal muscle (cm^2)	25 ± 5	29 ± 5*
CT imaging of the liver and the spleen		
Liver (HU)	59 ± 9	60 ± 8
Spleen (HU)	58 ± 4	56 ± 5*
L/S ratio	1.01 ± 0.16	1.07 ± 0.15*

Values are unadjusted means ± SD.
* $P < .01$.

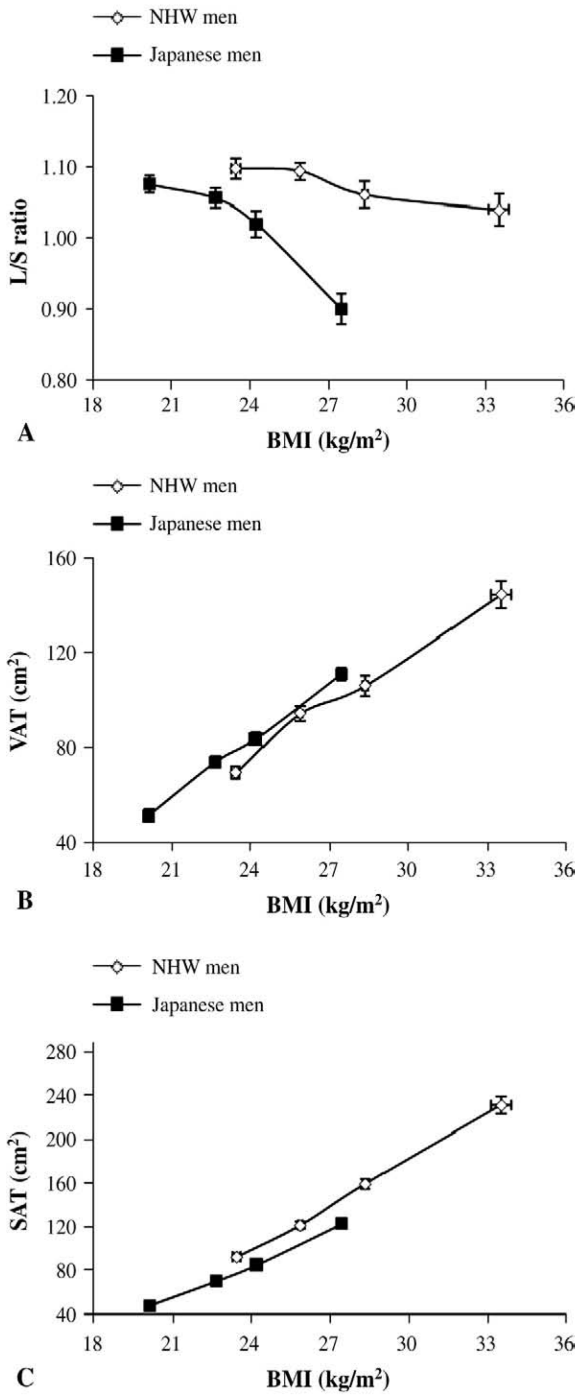

Fig. 1. Subjects were stratified by BMI in Japanese men (solid rectangle) and NHW men (open rectangle) separately; and mean values (±SEM) of BMI for each quartile are plotted against mean values (±SEM) of L/S ratio for respective quartiles (1A), those of VAT (1B), and those of SAT (1C). A, There was a significant ethnicity × BMI interaction for L/S ratio ($P < .01$); the decrease in L/S ratio was more robust in response to the increase in BMI, although in both populations, L/S ratio was negatively correlated with BMI ($P < .01$). B and C, There was no ethnicity × BMI interaction for VAT or SAT.

populations either together or separately. Because the proportion of subjects with habitual alcohol intake and the amount of daily ethanol intake were higher among Japanese compared with NHW men (68% vs 43% and 27 ± 29 vs 10 ± 14 g/d, respectively; both *P*s < .01), the group difference in the L/S ratio was also analyzed among subjects without habitual alcohol intake. The L/S ratio remained significantly lower in Japanese men (1.00 ± 0.17 vs 1.06 ± 0.16, unadjusted values; $P < .01$). When subjects with more than 30 g of daily ethanol intake were excluded, the L/S ratio remained significantly lower in Japanese men. Although the use of a glucose-lowering drug correlated significantly with lower L/S ratio ($P < .05$), this association disappeared after adjusting for diabetes status.

3.2. Ethnicity × BMI interaction for liver fat content

Because there was a difference in BMI by 4 kg/m^2, an estimate of total FM, we also analyzed the data stratifying the subjects by BMI. As shown in Fig. 1A, the change in liver fat content was more pronounced in response to increased BMI in Japanese compared with NHW men (*P* for interaction < .01), although both Japanese and NHW men had an inverse association of BMI with L/S ratio. Furthermore, as shown in Table 2, among Japanese, the prevalence of fatty liver (L/S ratio <1) was increased as BMI exceeded the overweight range to the Asian criteria of obesity [4] (BMI >23.5), whereas among NHW men, the prevalence was rather decreased in the range of BMI 23.5 to 25.0. The increase in VAT or SAT in response to the increase in BMI was similar between the 2 populations (Fig. 1B and C, respectively). As a result, the association of VAT as well as BMI with liver fat content was significantly different by ethnicity ($P < .01$).

3.3. Association of L/S ratio with metabolic parameters

The associations of L/S ratio with several metabolic parameters were next explored, focusing upon fasting TG, fasting glucose, HOMA-IR, and CRP. These associations are shown in Fig. 2, stratified by L/S ratio. Other metabolic profiles were described in detail previously [27].

Among both Japanese and NHW men, liver fat content had a significant positive correlation with fasting TG (Fig. 2A). Across L/S ratio, TG was similar between Japanese and NHW men, further indicating that liver fat is a good marker for reduced capacity to store excess energy (TG) inside the AT. Fasting glucose was much greater among subjects with fatty liver (L/S ratio <1) than those without fatty liver (L/S ratio >1) in each population (both *P*s < .01), although fasting glucose was not linearly correlated with liver fat content (Fig. 2B). Fasting glucose

Table 2
Prevalence of fatty liver (L/S ratio <1) stratified by obesity criteria for Asians

BMI	Japanese men (n = 314)	NHW men (n = 288)
<23.5	19.1% (30/157)	25.9% (7/27)
23.5-25	33.3% (22/66)	4.0% (2/50)
25-30	55.0% (44/80)	22.1% (30/136)
30+	73.0% (8/11)	42.7% (32/75)

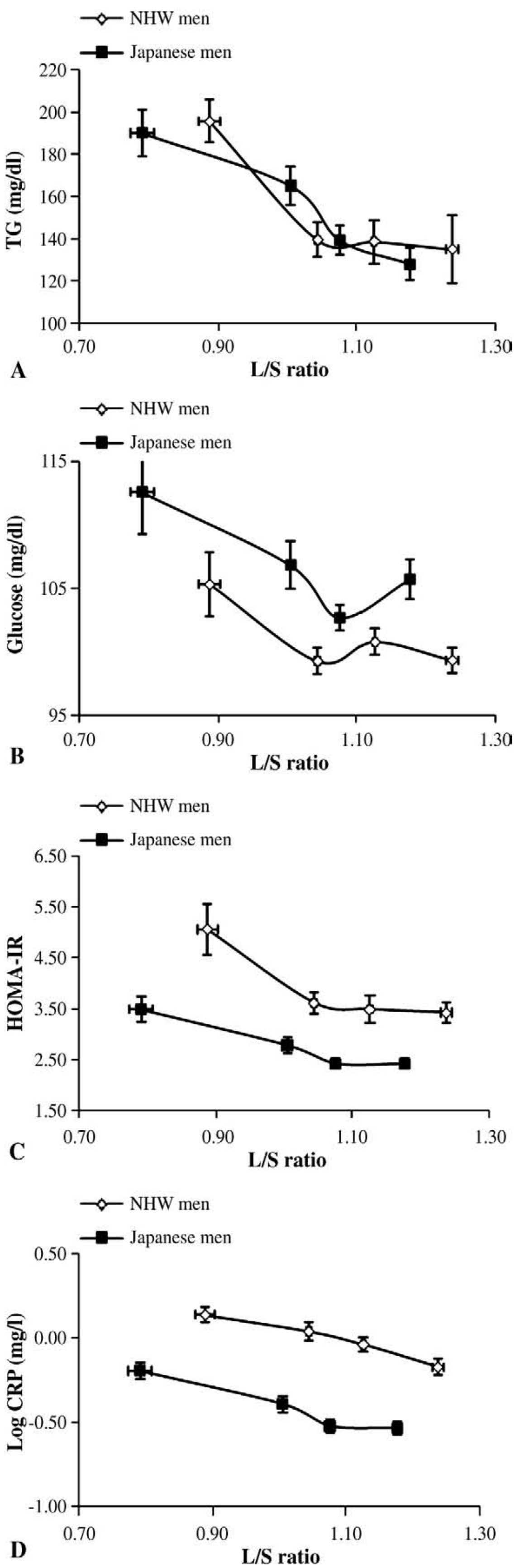

Fig. 2. Subjects were stratified by liver fat content (L/S ratio) in Japanese men (solid rectangle) and NHW men (open rectangle); and mean values (±SEM) of L/S ratio for each quartile are plotted against mean values (±SEM) of TG (in milligrams per deciliter, A), fasting glucose (B), HOMA-IR (C), and log CRP (in milligrams per deciliter, D), respectively, for respective quartiles. A, Serum fasting TG level was strongly correlated with L/S ratio, and the 2 plotted lines were superimposable with each other. B, There was no linear correlation between L/S ratio and fasting glucose. C and D, HOMA-IR and log CRP were strongly associated with L/S ratio; however, at any given L/S ratio, Japanese had lower HOMA-IR and lower log CRP ($P < .01$).

tended to be higher among Japanese than NHW men regardless of the degree of liver fat deposition. The HOMA-IR, an index of IR, and CRP, an index of systemic inflammation, showed strong correlations with L/S ratio (Fig. 2C and D, respectively) when analyzed with the 2 ethnic groups together or separately (all Ps < .01). At any given L/S ratio, however, both HOMA-IR and CRP were significantly lower among Japanese men (both Ps < .01).

4. Discussion

Our main findings are that liver fat content was higher in Japanese compared with NHW men and that liver fat increases with increasing BMI at a higher rate in Japanese men.

For Asians, including Japanese adults, *obesity* has been defined with a different BMI cutoff point (BMI >25) from the World Health Organization criteria (BMI >30 [3,4]). Only 3% of the Japanese population has a BMI greater than 30. This percentage has changed little during the last 40 years despite a recent rapid increase in incidence of obesity-associated metabolic risks such as dyslipidemia and type 2 diabetes mellitus in Japan [3,13]. On the other hand, about 20% of the population has a BMI greater than 25; and the percentage has increased more than 3-fold in the last 40 years [4]. These data imply that Asians have reduced capacity to store fat in response to positive net energy balance as a consequence of overeating and physical inactivity. Subsequently, BMI greater than 30 is rarely exceeded among Asians. In turn, ectopic fat such as liver fat [34] is rapidly accumulated among people with BMI greater than 25, which is consistent with our current findings (Fig. 1 and Table 2).

Few previous studies have reported ethnic differences in liver fat content between Asians and NHW, although some studies reported that African Americans have less liver fat as well as less VAT than NHW men [22,23]. Weston et al [23] reported that the incidence of fatty liver in Asians tended to be higher compared with NHW men, but the result was not conclusive because of the lack of direct statistical comparison for this ethnic difference [22]. In the current study, we have observed higher liver fat content among Japanese compared with NHW men in both adjusted and unadjusted values for the effect of age and BMI. Other possible confounding factors such as medication and alcohol drinking did not explain the observed ethnic difference.

It is unclear why the propensity for liver fat accumulation with increasing BMI differs between Japanese and NHW men, especially because visceral fat accumulation with increasing adiposity is similar between the 2 populations. It has been shown that liver fat content dynamically changes in response to moderate weight reduction. In addition, the absolute amount of fat accumulation is much less for the liver (<200 g) compared with visceral adiposity (~2 kg) or subcutaneous adiposity (~20 kg), provided there is plenty of blood circulation in the liver. [35] Therefore, because of the current homogenous population and indirect body composition assessment by BMI and CT imaging, only the ethnic difference in liver fat can be seen; and we may miss the potential difference in visceral/subcutaneous adiposity.

Emerging data convincingly demonstrate that hepatic fat content is strongly associated with metabolic risks [17,18,20,21] even among subjects with lipodystrophy [36] who do not have any AT. Indeed, we have found that liver fat content is strongly associated with higher TG, higher fasting insulin, and higher systemic inflammation in both populations. Moreover, TG levels in the liver and the blood are closely correlated in a similar manner regardless of the ethnicity, suggesting that liver fat is indeed a good marker to detect inability to store fat (TG) inside the AT. There seems to be, however, some ethnic differences in these associations as well.

The HOMA-IR, an index of IR, was much lower among Japanese compared with NHW men. This holds true at any given liver fat content. No previous epidemiologic study has compared IR between Japanese and NHW. Only 4 epidemiologic studies have examined the difference in IR between NHW and Japanese Americans, and the results were inconsistent [37-40]. Conversely, Japanese have higher liver fat than NHW men despite having a lower BMI and less IR, which is considered to be most important for hepatic fat accumulation. This may further emphasize that Japanese adults have had a phenotype for lower capacity to store fat in the body in response to positive net energy balance, a similar phenotype to acquired lipodystrophy [34]. Another possibility is that HOMA-IR varies between populations. In fact, when looking at the 75th percentile of HOMA-IR in nondiabetic Japanese (298/314) and NHW (277/288) men, it was significantly lower among Japanese compared with NHW (2.61 ± 1.19 vs 3.75 ± 2.22, $P < .01$).

C-reactive protein, an index of systemic inflammation, was also much lower among Japanese compared with NHW men at a given liver fat content, despite a very strong correlation with liver fat content in both populations. This is consistent with a prior report [41] and is probably due to genetic [42] and environmental factors. For the latter possibility, the quality of liver fat rather than the quantity might be important, mainly because of a difference in dietary intake. Although we do not have daily caloric intake data or macronutrient balance data, the INTERMAP Study showed that Japanese and NHW men have similar total daily energy intake per body weight (BW) (2300 kcal/d, 34 kcal/[kg BW] vs 2800 kcal/d, 31 kcal/[kg BW], respectively); yet Japanese compared with NHW men consume more carbohydrate as a percentage of total calories (52% vs 48%, respectively), less total and saturated fat, and less sugar [43]. The INTERMAP Study provides one of the most comprehensive international dietary data in middle-aged men and women in the United States, Japan, and other countries [43]. The INTERMAP Study also shows that omega-3 fatty acid intake is greater in Japanese men compared with NHW men (1.3 vs 0.7 g, respectively), whereas saturated fat intake is much less in Japanese men (16 vs 35 g, respectively). The results are consistent with our food questionnaire that shows that Japanese men had a much higher fish and soy consumption compared with NHW. One study showed that saturated fatty acid intake leads to steatohepatitis rather than simple steatosis [44]. In a mice model, saturated fatty acids in the liver may be associated with liver injury and endoplasmic reticulum stress [45], leading to inflammation and atherosclerosis [46]. This may be one reason why there is a much higher prevalence of fatty liver in Japanese men but less systemic inflammation and no reported higher incidence of steatohepatitis. Further study, including liver biopsy, will elucidate whether less inflammation in the liver in Japanese is indeed due to a difference in quality of fat, not quantity of fat in the liver.

The strength of this study includes that this is the first international comparison of liver fat content using population-based sample with rigid standardization of the assessment for body composition and metabolic parameters. The limitation of this study includes that the samples are limited to men in their 40s, and it is unclear whether this finding is applicable to women or different age groups. We used CT density as an index for liver fat, but this is not a quantitative measure. Liver attenuation can be caused by other conditions than the presence of fat. For example, liver glycogen content raises CT density [47]. Given the fact that Japanese consume more carbohydrate than NHW, however, this is unlikely to cause a lower CT density among Japanese and may rather minimize the difference between the 2 populations. We used a cross-sectional CT image for estimations of VAT and SAT volume; and because of homogeneity of sample population, we may miss the potential importance of VAT and SAT. We did not check hepatitis C virus infection, which is one of the major causes for liver steatosis. However, the prevalence of hepatitis C virus infection is similarly very low (< 2%) in both populations [48]; and this does not seem to affect the result.

In summary, we have observed that liver fat content was higher among Japanese compared with NHW men. In addition, Japanese have a greater propensity for liver fat disposition with a smaller increase in positive net energy balance, which is partly associated with similar metabolic risk such as TG levels between the 2 populations.

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