Metabolically Healthy Obesity, Presence or Absence of Fatty Liver, and Risk of Type 2 Diabetes in Japanese Individuals: Toranomon Hospital Health Management Center Study 20 (TOPICS 20)

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Objective: We investigated whether the metabolically healthy obese (MHO) phenotype was associated with an increased risk of the development of diabetes. If so, we aimed to determine what factors could explain this finding.

Design, Setting, and Participants: Studied were 8090 Japanese individuals without diabetes. Metabolic health status was assessed by common clinical markers: blood pressure, triglycerides, high-density lipoprotein-cholesterol, and fasting glucose concentrations. The cutoff value for obesity or normal weight (NW) was a body mass index of 25.0 kg/m^2.

Results: The 5-year incidence rate of diabetes was 1.2% (n = 58 of 4749) in metabolically healthy NW (MHNW) individuals, 2.8% (n = 20 of 719) in MHO individuals, 6.0% (n = 102 of 1709) in metabolically abnormal NW individuals, and 10.3% (n = 94 of 913) in metabolically abnormal obese individuals. Although MHO individuals had no or one metabolic factor, 47.8% had ultrasonographic fatty liver (FL). The MHO group had a significantly increased risk of diabetes compared with the MHNW group [multivariate adjusted odds ratio (OR) 2.23 (95% confidence interval [CI] 1.33, 3.75)], but this risk was attenuated after adjustment for FL. Compared with the MHNW/non-FL group, the risk of diabetes in the MHO/non-FL group was not significantly elevated [OR 1.01 (95% CI 0.35, 2.88)]. However, the MHO/FL and MHNW/FL groups had similarly elevated risks of diabetes [OR 4.09 (95% CI 2.20, 7.60) and 3.16 (1.78, 5.62), respectively].

Conclusions: Almost half of the MHO participants had FL, which partially explained the increased risk of diabetes among the obese phenotypes. The presence of FL should be evaluated to assess whether an individual was actually in a metabolically benign state for the prediction of diabetes.
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Overweight, obesity, and the presence of metabolic abnormalities increase the risk of development of type 2 diabetes (1, 2). The concept of metabolically healthy obesity or benign obesity, that is, obesity not associated with obesity-related metabolic abnormalities, is not new (3–5). Different phenotypes of obesity were associated

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Abbreviations: AUCROC, area under the receiver-operating characteristic curve; BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IFG, impaired fasting glucose; MANW, metabolically abnormal and normal weight; MAO, metabolically abnormal and overweight or obese; MHNW, metabolically healthy and normal weight; MHO, metabolically healthy and overweight or obese; OR, odds ratio.

with the presence of different clinical characteristics in human subjects (6–11). Consideration of different obese phenotypes has been an important clinical issue with regard to preventing and delaying the onset of type 2 diabetes (5, 12–14).

To date, several prospective cohort studies have investigated the combined effect of an elevated body mass index (BMI) and the presence of metabolic abnormalities (such as hyperglycemia, dyslipidemia, or hypertension) or insulin resistance in the development of diabetes (15–24). Results (15–24) suggest that a metabolically healthy obese phenotype might be associated with a nonsignificant or significant increased risk of the development of diabetes in comparison with metabolically healthy nonobese individuals as defined in each study. However, these studies used different definitions for metabolic health (healthy or unhealthy), and it is questionable whether the definitions of metabolic health or the categorization of obese phenotypes used in those previous studies (15–24) were adequate to predict future diabetes.

The absence of a universal definition for the metabolically healthy obese phenotype has been raised as an important issue. Lacking such a definition might result in the misclassification of some individuals who actually have a high-risk phenotype as having a low-risk phenotype. A study suggested that the clustering of overweight, insulin resistance, and fatty liver was common (20) and that liver enzymes or an accumulation of fat in liver could play important roles in differentiating obese phenotypes at high risk of future diabetes. Therefore, we aimed to investigate whether metabolically healthy obese individuals were significantly at high risk of developing type 2 diabetes compared with metabolically healthy nonobese (or nonoverweight) Japanese individuals. In addition, if the risk of developing diabetes in those with metabolically healthy obesity (defined by BMI and metabolic factors) was increased, we investigated what factors could partially explain that elevated risk.

Materials and Methods

Study participants

The Toranomon Hospital Health Management Center Study included a cohort consisting mainly of apparently healthy Japanese government employees who had annual examinations for routine health screening in addition to some participants from the general public. All participants were interviewed at each examination using standard questionnaires that gathered information on demographic characteristics, health-related habits, and medical history. A total of 29 584 individuals had a baseline health examination during the period from 1997 to 2002. Among the 29 584 individuals, we retrospectively reviewed data on 9344 individuals who had a reexamination at our center 5 years (2002–2007) after the initial examination. We excluded individuals with diabetes at the baseline examination (n = 397), those with positive test results for either hepatitis B surface antigen or hepatic C antibody (n = 345), or a self-reported history of liver cirrhosis (n = 8). Then data on 8618 individuals were available for the current analysis. After excluding individuals with missing data on self-report of lifestyle characteristics as shown in Table 1 (n = 528), this study included a total of 8090 individuals (5884 men and 2206 women) aged 24–80 years without diabetes. Diagnosis of type 2 diabetes was made according to the American Diabetes Association criteria of a fasting plasma glucose level of 7.0 mmol/L or greater, self-reported clinician-diagnosed diabetes, or glycated hemoglobin (HbA1c) of 6.5% or greater (≥48 mmol/mol) (25). The study protocol followed the Japanese Government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review Board at Toranomon Hospital.

Measurements of clinical markers

A standard questionnaire was used for assessing physical activity habits (any physical activity for 20–30 min or more at least once weekly); smoking habits; current alcohol consumption; and self-reported histories of dyslipidemia, hypertension, or diabetes. We calculated the average alcohol consumption (grams of ethanol per day) by multiplying the usual quantity of alcohol consumed per occasion by the frequency of alcohol consumption. Height and weight were measured without shoes or heavy clothing, and BMI was calculated. Blood pressure was measured by trained hospital staff with the subject in a sitting position. Blood samples were collected after an overnight fast (12 h), and measurements were made using an automatic clinical chemistry analyzer (LABOSPECT 008; Hitachi). Blood glucose, serum triglycerides, total cholesterol, and high-density lipoprotein (HDL)-cholesterol concentrations were measured by enzymatic methods. HbA1c was assessed by HPLC. The value for HbA1c was estimated as the National Glycohemoglobin Standardization Program value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society) (%) × 1.02 + 0.25% (26).

The diagnosis of fatty liver was based on the presence of an ultrasonographic pattern consistent with bright liver (brightness and posterior attenuation) with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins. Each ultrasonograph was performed by one of five technicians specialized in ultrasound (one ultrasonographer staffed each examination table). All ultrasonographic images obtained by the technicians were stored as photocopies. Two gastroenterologists expert in ultrasonography reviewed the photocopies and made the diagnosis of fatty liver without reference to any of the participants' data. Ultrasound tests were performed with a high-resolution, real-time scanner (model SSD-2000; Aloka Co, Ltd; Mode Logic-700 MR; GE-Yokokawa Medical Systems).

Assessment of metabolic health status

A cutoff point of BMI of 25 kg/m^2 was used to define overweight/obesity (≥ 25.0 kg/m^2) or normal weight (< 25.0 kg/m^2). We introduced cutoffs for four metabolic factors [impaired fasting glucose (IFG), hypertension, hypertriglyceridemia, low HDL-cholesterol concentration] using International Diabetes Federation definitions (27). Data on waist circumference, vis-

Table 1. Characteristics of Study Participants at the Baseline Examination

	MHNW	MHO	*P* Value[a]	MANW	MAO	*P* Value[b]
n, % of total participants	4749 (58.7)	719 (8.9)		1709 (21.1)	913 (11.3)	
Females	1680 (35.4)	156 (21.7)	<.001	267 (15.6)	103 (11.3)	.002
Parental history of diabetes, yes	615 (13.0)	107 (14.9)	.154	282 (16.5)	155 (17.0)	.755
Age, y	48.1 (8.1)	47.0 (7.6)	<.001	49.9 (8.3)	47.4 (7.4)	<.001
BMI, kg/m^2	21.5 (2.0)	26.6 (1.6)	<.001	22.6 (1.6)	27.1 (2.0)	<.001
Smoking habit			<.001			.138
Never	2672 (56.3)	352 (49.0)		753 (44.1)	374 (41.0)	
Former	935 (19.7)	176 (24.5)		444 (26.0)	232 (25.4)	
Current	1142 (24.0)	191 (26.6)		512 (30.0)	307 (33.6)	
Alcohol consumption			<.001			.377
None	969 (20.4)	105 (14.6)		263 (15.4)	125 (13.7)	
<20 g/d by women or <30 g/d by men	2609 (54.9)	433 (60.2)		879 (51.4)	492 (53.9)	
≥20 g/d by women or ≥30 g/d by men	1171 (24.7)	181 (25.2)		567 (33.2)	296 (32.4)	
Physically active, yes	2327 (49.0)	345 (48.0)	.611	816 (47.7)	439 (48.1)	.870
Hypertension[c]	1068 (22.5)	248 (34.5)	<.001	1246 (72.9)	716 (78.4)	.002
Triglycerides ≥1.7 mmol/L or treatment	308 (6.5)	86 (12.0)	<.001	990 (57.9)	602 (65.9)	<.001
HDL-cholesterol <1.03 mmol/L in males or <1.29 mmol/L in females	352 (7.4)	64 (8.9)	.160	704 (41.2)	418 (45.8)	.024
Fasting plasma glucose 5.6–6.9 mmol/L	454 (9.6)	106 (14.7)	<.001	1009 (59.0)	559 (61.2)	.277
Total number of metabolic factors			<.001			<.001
None	2567 (54.1)	215 (29.9)		0 (0)	0 (0)	
One factor	2182 (45.9)	504 (70.1)		0 (0)	0 (0)	
Two factors	0 (0)	0 (0)		1238 (72.4)	524 (57.4)	
Three factors	0 (0)	0 (0)		411 (24.0)	309 (33.8)	
Four factors	0 (0)	0 (0)		60 (3.5)	80 (8.8)	
γ-Glutamyltransferase, U/L	27 (18, 44)	45 (27, 75)	<.001	43 (27, 73)	63 (40, 102)	<.001
Alanine aminotransferase, U/L	18 (14, 24)	26 (19, 37)	<.001	23 (17, 31)	32 (23, 48)	<.001
Fatty liver, yes	536 (11.3)	344 (47.8)	<.001	544 (31.8)	650 (71.2)	<.001

Data are n (percentage), mean ± SD or median (25th, 75th).

[a] *P* values between MHNW and MHO groups. *P* values were tested by a χ^2, median test, or *t* test.

[b] *P* values between MANW and MAO groups. *P* values were tested by a χ^2 test, median test, or *t* test.

[c] Hypertension was indicated by systolic blood pressure of 130 mm Hg or greater, diastolic blood pressure of 85 mm Hg or greater, or medical treatment.

ceral fat, fasting insulin, and C-reactive protein concentrations were not available for study participants, although we acknowledge that these markers can be used to define metabolic health (12–14). Individuals with a systolic blood pressure of 130 mm Hg or greater and/or a diastolic blood pressure of 85 mm Hg or greater or who were under medical treatment were considered to have hypertension. Elevated triglycerides was indicated by 150 mg/dL (1.7 mmol/L) or greater or treatment of hyperlipidemia, and reduced HDL-cholesterol was indicated by less than 40 mg/dL (1.03 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women. IFG was indicated by 100–125 mg/dL (5.6–6.9 mmol/L).

In the context of obesity, a metabolically healthy state was considered if none or one of the metabolic factors based on the International Diabetes Federation definition was present, and a metabolically abnormal state was declared if two or more metabolic factors were present (27). Then participants were categorized at the baseline examination into four phenotypes: 1) metabolically healthy and normal weight (MHNW), 2) metabolically healthy and overweight or obese (MHO), 3) metabolically abnormal and normal weight (MANW), or 4) metabolically abnormal and overweight or obese (MAO). Changes in the prevalence rate of overweight or obesity, metabolic health, and fatty liver among the four phenotypes were examined 5 years after the baseline examination.

Statistical analysis

A logistic regression analysis was performed to calculate odds ratios (ORs) for the development of diabetes. To investigate the impact of factors that influenced the association between the four phenotypes and diabetes, we analyzed data using models with the following adjustments: age and sex (model 1); age, sex, parental history of diabetes, smoking habit, physical activity habit, and alcohol consumption (model 2); model 2 + IFG (model 3); model 2 + log-transformed γ-glutamyltransferase and log-transformed alanine aminotransferase (ALT) (model 4); and model 2 + fatty liver (model 5). We also performed an additional analysis when we included the IFG state into model 2 and assessed the effect of liver enzymes (model 6) or fatty liver (model 7). We also assessed the area under the receiver-operating characteristic curve (AUCROC) for future diabetes and net reclassification improvement (28) by the use of three risk categories (<5%, 5%–15%, and >15%) by adding an assessment of fatty liver into a prediction model for the development of diabetes that included the obese phenotypes (four groups), age, sex, parental history of diabetes, and IFG. An analysis was performed with IBM SPSS Statistics version 19 or STATA software version 11 (StataCorp). The statistical significance was considered for $P < .05$.

Results

Among all participants, the prevalence of MHNW, MHO, MANW, or MAO was 58.7% (n = 4749), 8.9% (n = 719), 21.1% (n = 1709), or 11.3% (n = 913), respectively. Of the overweight/obese individuals, 44.1% (n = 719 of 1632) were not classified as metabolically abnormal based on the definition used in this study (Table 1). Of metabolically healthy individuals, 13.1% (n = 719 of 5468) were overweight or obese. Compared with MHNW individuals, MHO individuals were more likely to be male and younger and have had a history of a smoking habit or a current drinking habit, have elevated values for liver enzymes, have a higher prevalence of fatty liver, or have a higher prevalence of 1 metabolic factor.

Of the total participants, 25.6% (n = 2074 of 8090) had fatty liver, and the presence of fatty liver was high at 47.8% among the MHO individuals. When we performed logistic regression analysis and calculated the age- and sex-adjusted ORs for fatty liver at the baseline examination, results showed that compared with MHNW individuals, MHO, MANW, and MAO individuals had a significantly elevated OR [95% confidence interval (CI)] of 6.70 (5.62, 7.99), 3.22 (2.80, 3.70), and 16.8 (14.1, 19.9), respectively. Results were fundamentally the same if we calculated age- and sex-adjusted ORs among the 5875 individuals who consumed less than 20 g/d of alcohol (for women) or less than 30 g/d of alcohol (for men) [MHO, OR 7.52 (95% CI 6.13, 9.22); MANW, OR 3.75 (95% CI 3.17, 4.42); and MAO, OR 20.1 (95% CI 16.2, 24.9) compared with the MHNW phenotype].

During the 5-year follow-up period (median 1824 d, range 1473–2178 d), 274 individuals developed diabetes (83 had a history of clinician diagnosed diabetes). The crude incidence rate of diabetes was 1.2% (n = 58 of 4749) in MHNW, 2.8% (n = 20 of 719) in MHO, 6.0% (n = 102 of 1709) in MANW, and 10.3% (n = 94 of 913) in MAO phenotypes. Among the MHO individuals, 85.1% remained overweight (BMI $\geq$ 25 kg/m^2) 5 years after the baseline examination, and their metabolic risk profiles had worsened during that period (Supplemental Table 1). Of the MHO group, 34.2% (n = 246 of 719) had either type 2 diabetes or two or more metabolic abnormalities at the follow-up examination. Therefore, these individuals were no longer metabolically healthy 5 years after the baseline examination. In the MHNW group, 16.5% (n = 784 of 4749) newly developed either diabetes or a metabolically abnormal state. Of the MANW group, 9.3% (n = 159 of 1709) had a BMI of 25.0 kg/m^2 or greater at the follow-up examination, whereas 34.1% (n = 582 of 1709) had not developed diabetes and had achieved a metabolically healthy state. Of the MAO individuals at the baseline examination, we observed that 26.0% (n = 237 of 913) had not developed diabetes and had achieved a metabolically healthy state (MHNW or MHO) at the follow-up examination.

Age- and sex-adjusted OR for the development of diabetes was 2.29 (95% CI 1.37, 3.84) for MHO individuals, 4.62 (95% CI 3.31, 6.44) for MANW individuals, and 8.86 (95% CI 6.29, 12.5) for MAO individuals compared with MHNW individuals (model 1 in Table 2). Adjustment for lifestyle factors and parental history of diabetes did not greatly alter the association (model 2). After we adjusted for the presence of IFG at the baseline examination (model 3), ORs were attenuated, especially for the metabolically abnormal individuals [MANW, OR 1.51 (95% CI 1.04, 2.19); MAO, OR 2.87 (95% CI 1.96, 4.20)], although these phenotypes were still associated with a significantly increased risk of diabetes.

We performed a sensitivity analysis of individuals without IFG at the baseline examination, although only a small number of incident cases of diabetes was found among these individuals (n = 56 of 5962). Results showed that the age- and sex-adjusted OR (95% CI) for the development of diabetes was 2.99 (1.42, 6.33) in MHO (cases/total, n = 10 of 613), 2.23 (1.05, 4.72) in MANW (n = 10 of 700), or 6.06 (2.96, 12.4) in MAO (n = 12 of 354) compared with MHNW individuals (n = 24/4295). Adjustment for liver enzymes in model 4 slightly attenuated the OR for diabetes in the MHO phenotype. The MHO individuals did not have a significantly increased OR independently of the presence of fatty liver in model 5 [OR 1.54 (95% CI 0.90, 2.62)], whereas the MANW and MAO individuals had a significantly increased OR of 3.59 (95% CI 2.55, 5.06) and 4.96 (3.39, 7.25), respectively, compared with the MHNW individuals. Only MAO individuals had a significantly increased risk of the development of diabetes shown by the results of model 6 [OR 1.92 (95% CI 1.28, 2.87)] or model 7 [OR 1.73 (1.15, 2.60)]. When we calculated the ORs among the individuals with an alcohol consumption of less than 20 g/d (for women) or less than 30 g/d (for men), the MHO group did not have an elevated risk of diabetes in model 7, with an adjusted OR 1.05 (95% CI 0.54, 2.06).

We then assessed the combined effect of metabolic health status and fatty liver at the baseline examination on the development of diabetes (Figure 1). The MHNW/without fatty liver group had the lowest incidence rate of diabetes (0.9%), whereas the MHO/without fatty liver group had a similarly low incidence rate of diabetes (1.1%). Among the MHO/without fatty liver group (n = 375), only four had developed diabetes. On the other hand, the MHO/fatty liver group had an elevated incidence rate (4.7%) as did the MHNW/fatty liver group (3.5%). The incidence rate of diabetes was markedly high

Table 2. ORs for the Development of Type 2 Diabetes at 5 Years After the Baseline Examination According to Metabolic Phenotypes

Model	MHNW	MHO	MANW	MAO
Total participants				
Cases/n	58/4749	20/719	102/1709	94/913
1. Age, sex	1.00 (Referent)	2.29 (1.37, 3.84)	4.62 (3.31, 6.44)	8.86 (6.29, 12.5)
2. Lifestyle factors, parental diabetes[a]	1.00 (Referent)	2.23 (1.33, 3.75)	4.41 (3.16, 6.17)	8.50 (6.02, 12.0)
3. IFG[b]	1.00 (Referent)	1.92 (1.13, 3.26)	1.51 (1.04, 2.19)	2.87 (1.96, 4.20)
4. Liver enzymes[c]	1.00 (Referent)	1.70 (1.003, 2.88)	3.82 (2.72, 5.37)	5.57 (3.85, 8.07)
5. Fatty liver[d]	1.00 (Referent)	1.54 (0.90, 2.62)	3.59 (2.55, 5.06)	4.96 (3.39, 7.25)
6. IFG, liver enzymes[e]	1.00 (Referent)	1.50 (0.87, 2.56)	1.35 (0.92, 1.96)	1.92 (1.28, 2.87)
7. IFG, fatty liver[f]	1.00 (Referent)	1.32 (0.76, 2.27)	1.28 (0.88, 1.87)	1.73 (1.15, 2.60)
Participants without excessive alcohol consumption				
Cases/n	43/3578	13/538	70/1142	73/617
1. Age, sex	1.00 (Referent)	2.02 (1.08, 3.79)	4.78 (3.22, 7.07)	10.5 (7.05, 15.6)
2. Lifestyle factors, parental diabetes[a]	1.00 (Referent)	1.97 (1.05, 3.70)	4.57 (3.08, 6.79)	10.0 (6.71, 14.9)
3. IFG[b]	1.00 (Referent)	1.74 (0.91, 3.31)	1.63 (1.05, 2.53)	3.49 (2.24, 5.46)
4. Liver enzymes[c]	1.00 (Referent)	1.49 (0.79, 2.84)	4.06 (2.72, 6.06)	6.52 (4.22, 10.1)
5. Fatty liver[d]	1.00 (Referent)	1.22 (0.64, 2.35)	3.45 (2.29, 5.18)	5.19 (3.33, 8.08)
6. IFG, liver enzymes[e]	1.00 (Referent)	1.38 (0.71, 2.65)	1.47 (0.94, 2.29)	2.32 (1.44, 3.74)
7. IFG, fatty liver[f]	1.00 (Referent)	1.05 (0.54, 2.06)	1.26 (0.80, 1.98)	1.81 (1.11, 2.94)

Alcohol consumption was indicated by three groups (none, alcohol $<$ 20 g by women or $<$ 30 g by men, and alcohol $\geq$ 20 g by women or $\geq$ 30 g by men) among total participants or two groups (none or alcohol $<$ 20 g by women or $<$ 30 g by men) among participants without excessive alcohol consumption.

[a] Model 2: age, sex, parental history of diabetes, smoking habit (never, former, current), physical activity habit (yes), and alcohol consumption.

[b] Model 3: model 2 + IFG (fasting glucose 5.6–6.9 mmol/L).

[c] Model 4: model 2 + log-transformed γ-glutamyltransferase and log-transformed alanine aminotransferase.

[d] Model 5: model 2 + fatty liver.

[e] Model 6: model 3 + log transformed γ-glutamyltransferase and log-transformed alanine aminotransferase.

[f] Model 7: model 3 + fatty liver.

at 8.5% in the MANW/fatty liver group and 12.6% in the MAO/fatty liver group.

Compared with the lowest risk group (MHNW/without fatty liver group), the MHO/without fatty liver group had an adjusted OR of 1.01 (95% CI 0.35, 2.88) in multivariate-adjusted model 2 (Table 3). Conversely, the MHO/fatty liver group had an OR of 4.09 (95% CI 2.20, 7.60) for future diabetes. The OR in the MAO/fatty liver group was attenuated after adjustment for IFG in the multivariate-adjusted model 2, although the OR was the highest across the eight groups. If we compared the risk of diabetes among individuals with fatty liver, the MHO/fatty liver group did not have a significantly increased risk of future diabetes compared with the MHNW/fatty liver group (Supplemental Table 2).

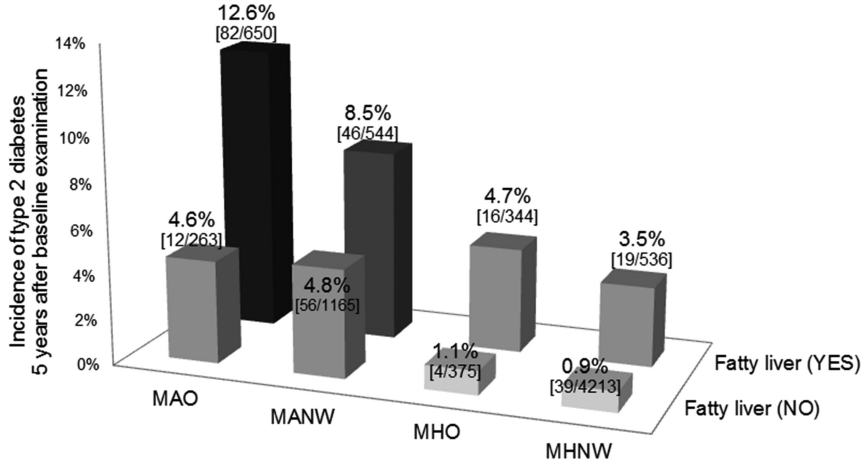

Figure 1. Combined effect of the presence of fatty liver and obese phenotypes on the incidence rate of type 2 diabetes at 5 years after the baseline examination. Data were percentages (cases/total n for each group). A cutoff point of a BMI of 25 kg/m^2 was used to define overweight/obesity ($\geq$ 25.0 kg/m^2) or normal weight ($<$ 25.0 kg/m^2). Metabolic health was assessed by four factors (impaired fasting glucose, hypertension, hypertriglyceridemia, and low HDL-cholesterol concentration) using the International Diabetes Federation definitions. A metabolically healthy state was considered if none or one of the metabolic factors was present and a metabolically abnormal state was declared if two or more metabolic factors were present.

A prediction model with age, sex, parental history of diabetes, IFG, and obese phenotypes had an AUCROC of 0.836 (95% CI 0.814, 0.857) for the development of diabetes. The AUCROC was slightly but a significantly ($P < .001$) improved when we added the assessment of fatty liver into the model, with an AUCROC of 0.850 (95% CI 0.829,

Table 3. ORs for the Development of Type 2 Diabetes According to the Combination of Fatty Liver and Obese Phenotypes

	MHNW	MHO	MANW	MAO
Age- and sex-adjusted model				
Fatty liver (no)	1.00 (Referent)	1.17 (0.42, 3.30)	4.92 (3.23, 7.49)	4.86 (2.51, 9.44)
Fatty liver (yes)	3.86 (2.20, 6.76)	5.31 (2.92, 9.66)	9.30 (5.94, 14.5)	15.6 (10.4, 23.4)
Multivariate-adjusted model 1[a]				
Fatty liver (no)	1.00 (Referent)	1.14 (0.40, 3.21)	4.69 (3.07, 7.16)	4.68 (2.41, 9.11)
Fatty liver (yes)	3.76 (2.14, 6.61)	5.18 (2.84, 9.47)	8.82 (5.62, 13.8)	15.0 (9.97, 22.5)
Multivariate-adjusted model 2[b]				
Fatty liver (no)	1.00 (Referent)	1.01 (0.35, 2.88)	1.54 (0.98, 2.43)	1.49 (0.74, 2.97)
Fatty liver (yes)	3.16 (1.78, 5.62)	4.09 (2.20, 7.60)	3.11 (1.92, 5.03)	5.03 (3.24, 7.80)

[a] Multivariate-adjusted model 1 included age, sex, parental history of diabetes, smoking habit (never, former, current), physical activity habit (yes), and alcohol consumption (none, alcohol < 20 g by women or < 30 g by men, and alcohol ≥ 20 g by women or ≥ 30 g by men).

[b] Multivariate-adjusted model 2 included age, sex, parental history of diabetes, smoking habit, physical activity habit, alcohol consumption, and impaired fasting glucose (fasting glucose 5.6–6.9 mmol/L).

0.871). The net reclassification improvement was 13.6% (95% CI 7.5%, 19.7%) by introducing the assessment of fatty liver in the prediction model.

Discussion

In this study of Japanese individuals, the MHO phenotype, defined by a BMI of 25 kg/m^2 or greater with no or one metabolic factor (hypertension, dyslipidemia, or IFG), was associated with a significantly higher risk of type 2 diabetes than the MHNW phenotype. At baseline, about half of the MHO individuals had ultrasonographic evidence of fatty liver, which is an established risk factor for diabetes (29, 30). The definition of metabolically healthy in this study did not differentiate according to the absence of liver fat. On the other hand, the MHO group without fatty liver had a low incidence of diabetes, and the OR was not significantly different from that for the MHNW group without fatty liver. Our findings suggest that adding information on the presence of fatty liver determined by ultrasonographic measurement into the assessment of MHNW, MHO, MHNW, and MAO phenotypes would provide clinicians and health care professionals with more precise information for predicting the risk of developing diabetes.

Studies of obese individuals suggested that the MHO group had a more favorable distribution of low visceral fat, although the total fat mass was similar between MHO and MAO (4, 8). Although we had no data on visceral fat in this study, results of a previous study indicated that ectopic fat in the liver might be more important than visceral fat in the determination of metabolically benign obesity (7). That report also showed that an obese-insulin sensitive group had less fat accumulation in the liver than a similar obese-insulin resistance group (7). A study of monozygotic twins showed that whether there was an accumulation of fat in liver influenced the presence of metabolic disturbances in obese individuals (10). A cross-sectional study of Koreans reported that MHO individuals had a high probability of fatty liver but not of preclinical atherosclerosis as assessed by the coronary artery calcification score (11). We could not determine why MHO individuals were more likely to have fatty liver at the baseline examination, and we observed that results were not influenced by excessive alcohol intake.

It was reported that fat accumulation in the liver induced hyperglycemia, dyslipidemia, subclinical inflammation, and the secretion of substances called hepatokines (such as fetuin-A) that would induce insulin resistance (31). However, a review showed that among individuals with fatty liver, 37% did not have metabolic syndrome, prediabetes, or diabetes (32). The present results showed that even in MHNW and MHO individuals, the incidence rate of diabetes was increased in the presence of fatty liver. A prospective study that investigated clustering of insulin resistance, overweight/obesity, and fatty liver showed that the clustering of these markers markedly increased the odds of developing diabetes (20). Our study introduced four metabolic factors commonly available in clinical settings to define whether an individual was metabolically healthy or unhealthy rather than using the degree of insulin resistance. Using routinely available metabolic parameters, we showed that MAO individuals who also had ultrasonographic fatty liver had a markedly elevated risk of future diabetes. Our findings may contribute to identifying patients with metabolically malignant fatty liver (32) that may substantially increase the risk of future diabetes.

Although several studies provided longitudinal data on the risk of developing diabetes in the four obese phenotypes that we examined, it is difficult to directly compare our results with those of other studies because the defini-

tion of metabolic health and definitions used for the diagnosis of diabetes differed among studies (15–24). However, the MHO phenotype defined in each study was associated with an increased risk of diabetes (15–19, 21–24), which was in line with our results. While we were revising our manuscript, a meta-analysis of seven cohort studies (15–17, 19, 21, 23, 24) and original data on elderly English adults was published (33); MHO individuals had an approximately 4-fold increased risk of future diabetes than MHNW individuals (33). Two recent studies also reported that MHO individuals had an increased risk of type 2 diabetes (34, 35). On the other hand, it was suggested that healthy obesity might be a transient state (16, 21); thus, the impact of changes in obese phenotypes on the risk of developing diabetes should be further investigated in detail. Our results showed that a relatively large number of MHO individuals were classified as being metabolically abnormal or having newly developed diabetes 5 years after the baseline examination. This suggests that although some obese individuals were metabolically healthy at the baseline examination, the application of diabetes preventive strategies such as alterations in diet and physical activity would be important in overweight-obese individuals in preventing or delaying the development of diabetes.

It is not conclusive whether different lifestyle interventions that considered metabolically benign and malignant obesity would be effective in preventing diabetes (36, 37); this area needs further investigation. Whether metabolically normal but obese individuals are at increased risk of cardiovascular and all-cause mortality is also an important issue (38). Nonetheless, we observed that the risk of diabetes was higher in all three phenotypes in comparison with the MHNW phenotype. Even a small weight gain was reported to result in the development of nonalcoholic fatty liver disease (39); thus, weight management should be important in preventing metabolic abnormalities.

Strengths of our study include the large number of participants both at baseline and at follow-up and the ability to describe changes in metabolic health and obesity during a 5-year follow-up. Although our previous reports on the Toranomon Hospital Health Management Center Study project did not address the association of fatty liver with the increased risk of future diabetes among apparently healthy individuals without diabetes, the present findings underscore the importance for clinicians of the presence of fatty liver in assessing an individual's potential to develop diabetes.

Limitations were a lack of data on waist circumference, inflammatory markers, insulin concentrations, or oral glucose tolerance tests. Therefore, we could not perform sensitivity analyses to confirm the consistency of our results when different definitions of metabolic health were used in this study population. Because the diagnosis of fatty liver was by ultrasonography, the presence of fatty liver in all individuals might not have been captured. That our study patients did not undergo a histological or morphological assessment by peritoneoscopy or liver biopsy was also a limitation. Nonetheless, a meta-analysis found that the sensitivity and specificity of ultrasound for detecting moderate-severe fatty liver were 84.8% and 93.6%, respectively, when using histology as the gold standard (40). In addition, Asian individuals are more likely to have a higher percentage of fat or visceral adipose tissue at a given BMI than Europeans (1). Further studies should be conducted with detailed data on body composition such as visceral fat. Because our study participants consisted of apparently healthy Japanese individuals who underwent a health examination, which indicates concern about health, some participants might have made lifestyle changes based on results of the health examination to prevent the development of metabolic abnormalities. Also, the retrospective design of our study (ie, historical cohort study) did not negate the possibility of influences by unknown confounding factors on our observations. Because our study participants were predominantly males, it should be investigated whether these findings would apply to other populations consisting mainly of women. In addition, examination is needed of a possible sex difference in the association of fatty liver and metabolic risk in developing diabetes.

In conclusion, almost half of the MHO individuals had accumulated fat in the liver as assessed by ultrasonography at the baseline examination, and this observation partially explained the increased risk of diabetes among the MHO individuals. The presence of fatty liver should be evaluated to assess whether an individual was actually in a metabolically benign state in predicting risk of future diabetes.

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