Fatty liver with metabolic disorder, such as metabolic dysfunction-associated fatty liver disease, indicates high risk for developing diabetes mellitus

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Keywords
Diabetes mellitus, Fatty liver, Metabolic disease

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J Diabetes Investig 2022; 13: 1245–1252
doi: 10.1111/jdi.13772

ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is diagnosed after excluding other liver diseases. The pathogenesis of NAFLD when complicated by other liver diseases has not been established completely. Metabolic dysfunction-associated fatty liver disease (MAFLD) involves more metabolic factors than NAFLD, regardless of complications with other diseases. This study aimed to clarify the effects of fatty liver occurring with metabolic disorders, such as MAFLD without diabetes mellitus (DM), on the development of DM.

Materials and Methods: We retrospectively assessed 9,459 participants who underwent two or more annual health check-ups. The participants were divided into the MAFLD group (fatty liver disease with overweight/obesity or non-overweight/obesity complicated by metabolic disorders), simple fatty liver group (fatty liver disease other than MAFLD group), metabolic disorder group (metabolic disorder without fatty liver disease), and normal group (all other participants).

Results: The DM onset rates in the normal, simple fatty liver, metabolic disorder, and MAFLD groups were 0.51, 1.85, 2.52, and 7.36%, respectively. In the multivariate analysis, the MAFLD group showed a significantly higher risk of DM onset compared with other three groups ($P < 0.01$). Additionally, the risk of DM onset was significantly increased in fatty liver disease with overweight/obesity or pre-diabetes ($P < 0.01$).

Conclusions: Fatty liver with metabolic disorders, such as MAFLD, can be used to identify patients with fatty liver disease who are at high risk of developing DM. Additionally, patients with fatty liver disease complicated with overweight/obesity or pre-diabetes are at an increased risk of DM onset and should receive more attention.

INTRODUCTION

Certain changes to a person’s lifestyle, including increased dietary and fat intake and decreased physical activity, can induce various metabolic diseases. Among them, diabetes mellitus (DM) increases the incidence of cardiovascular disease and cancer1–4; furthermore, it is considered to have a significant effect on healthy life expectancy5. Therefore, there is a need to identify high-risk populations for DM and to provide lifestyle interventions.
Nonalcoholic fatty liver disease (NAFLD) affects the development of DM. However, since NAFLD is diagnosed after excluding other liver diseases, the pathogenesis of NAFLD when complicated by other liver diseases has not been established completely. Furthermore, since there are numerous patients with fatty liver disease, providing interventions for all of them is difficult; moreover, there is a need to stratify their risk of the development of DM.

Metabolic dysfunction-associated fatty liver disease (MAFLD), which is defined as fatty liver disease combined with obesity, diabetes, and metabolic diseases, regardless of the presence of other liver diseases, was proposed by the American Gastroenterological Association and the European Association for the Study of the Liver in 2020. MAFLD is considered a fatty liver disease containing more metabolic factors than NAFLD; however, the impacts of MAFLD on the development of various metabolic disorders remain unclear. Therefore, we aimed to clarify the effects of fatty liver with some metabolic diseases, including MAFLD, on the development of DM.

MATERIALS AND METHODS

This community-based longitudinal cohort study examined the medical records of 9,817 Japanese participants (4,793 men and 5,024 women). The participants were aged 21–78 years and underwent two or more annual health examinations at the Ehime General Health Care Association from April 2003 to March 2017. Annual health examinations were conducted to record the medical history and prescribed medications, perform body measurements, and assess routine biochemical variables.

The body mass index (BMI; kg/m²) was calculated using body weight and height, measured wearing only a light gown. Blood pressure was assessed with an automatic sphygmmomanometer in a seated position. Blood samples were collected after fasting for >10 h. The risk of diabetes was determined based on the levels of fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c). Liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were analyzed. Lipid profiles were determined by assessing triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels. Furthermore, creatinine (Cr), hepatitis B surface antigen (HBs-Ag), and hepatitis C antibody (anti-HCV) levels were measured. Before the physical examination, health workers asked the participants to complete a questionnaire assessing their medical history; prescribed medications; family history of DM to the second degree; health-related behaviors, including exercise (no habit or awareness of exercise vs periodic exercise) and snacking habits (no snacking vs snacking ≥1 time/day); alcohol consumption (men: ≥210 g/week, women: ≥140 g/week), and smoking status. An experienced technician diagnosed fatty liver disease by abdominal ultrasonography without considering the participants’ data. Of the four fatty liver disease diagnostic criteria (hepatorenal echocardiographic contrast, liver brightness, deep attenuation, and vascular blurring), fatty liver disease was diagnosed based on hepatorenal contrast and liver brightness.

Definitions

The MAFLD group comprised participants with fatty liver disease who were overweight/obese (BMI ≥23 kg/m²) or non-overweight/obese with a metabolic disorder. The criteria for metabolic disorders were defined, based in part, on the criteria for MAFLD, and the diagnosis was based on the presence of two or more of the following metabolic risks: hypertension: blood pressure ≥130/85 mmHg or anti-hypertension drug treatment; high TG levels (TG ≥1.70 mM or lipid-lowering drug treatment; low HDL-C levels (HDL-C <1.04 mM for men and <1.30 mM for women); pre-diabetes: impaired fasting glucose (fasting glucose levels 5.55–6.94 mM) or HbA1c between 5.7% and 6.4% without anti-diabetes treatment. The simple fatty liver group comprised participants with fatty liver disease other than the MAFLD group, while the metabolic disorder group comprised participants with metabolic disorders without fatty liver disease. The remaining participants were included in the normal group.

Diabetes mellitus onset was identified when the blood test examination and questionnaire at the health check-up visit revealed fasting glucose levels >6.99 mM, HbA1c ≥6.5%, or initiation of anti-diabetes drug treatment.

After examination of the medical records, 359 patients with diabetes were excluded using the following exclusion criteria: currently receiving antidiabetic medications (n = 120), fasting glucose levels >6.99 mM (n = 267), or HbA1c ≥6.5% (n = 310) (Figure 1). The final analysis comprised 9,459 participants (4,509 men and 4,950 women) of Ehime University Hospital (Figure 1). The observed mean duration was 5.53 ± 3.53 years (men: 5.32 ± 3.53 years, women: 5.73 ± 3.51 years). This study was approved by the Research Ethics Committee of Ehime University Hospital following the tenets of the Declaration of Helsinki and its later amendments (approval number: 1709007; University Hospital Medical Information Network ID: UMIN00001953), and was conducted in compliance with the Guidelines for Good Clinical Practice and local.
RESULTS

Characteristics of the participants

Table 1 shows the baseline characteristics of each group. The onset rates of diabetes mellitus in the normal, simple fatty liver, metabolic disorder, and MAFLD groups were 0.51, 1.85, 2.52, and 7.36%, respectively (Table 1). Compared with the normal group, the other groups had a significantly higher proportion of males; were older; and had higher BMIs; increased BP and FPG, HbA1c, AST, ALT, Cre levels, and TG; lower HDL-C levels; a lower proportion of snacking habits; and a higher proportion of current smokers (Table 1). The metabolic disorder group had a higher proportion of participants who performed periodic exercise and were drinkers than the other groups (Table 1). There were 128 patients with HBs-Ag, 91 patients with anti-HCV, and 752 drinkers (Table 1).

The endpoint characteristics were similar to the baseline characteristics (Table 2). Compared with the normal group, the other groups had higher BMIs; increased BP and FPG, HbA1c, AST, ALT, Cre, and TG levels; lower HDL-C levels; a lower proportion of individuals with snacking habits; and a higher proportion of current smokers (Table 2). The metabolic disorder group had a higher proportion of participants who performed periodic exercise and were drinkers than the other groups (Table 2).

Table 1 | Baseline characteristics

|                  | Normal (n = 4,930) | Simple fatty liver (n = 271) | Metabolic disorder (n = 2,377) | MAFLD (n = 1,881) | P     |
|------------------|-------------------|-----------------------------|-------------------------------|-------------------|------|
| Sex (male), %    | 1,482 (30.1)      | 151 (55.7)                  | 1,450 (61.0)                  | 1,426 (75.8)      | <0.01|
| Age, years       | 40 (34–47)        | 42 (36–49)*                 | 45 (37.5–52)*                 | 44 (38–51)*       | <0.05|
| BMI, kg/m²       | 20.4 (19–21.5)    | 21.8 (20.7–22.3)*           | 24.1 (23.2–25.5)*             | 26 (24.3–28.1)*   | <0.01|
| SBP, mmHg        | 105 (87–114)      | 110 (101–119)*              | 118 (108–132)*                | 123 (112–135)*    | <0.01|
| DBP, mmHg        | 65 (59–72)        | 67 (63–75)*                 | 74 (66–84)*                   | 77 (69.5–87)*     | <0.01|
| FPG, mM          | 4.94 (4.66–5.16)  | 5.11 (4.89–5.38)*           | 5.22 (4.94–5.55)*             | 5.38 (5.11–5.72)* | <0.01|
| HbA1c, %         | 5.4 (5.1–5.6)     | 5.5 (5.2–5.7)*              | 5.5 (5.2–5.7)*                | 5.6 (5.4–5.8)*    | <0.01|
| AST, IU/L        | 19 (16–22)        | 20 (17–24)*                 | 20 (17–24)*                   | 24 (20–30)*       | <0.01|
| ALT, IU/L        | 14 (12–19)        | 21 (14–30)*                 | 19 (14–26)*                   | 30 (21–45)*       | <0.01|
| Cre, µM          | 61.9 (53.0–70.7)  | 61.9 (53.0–77.8)*           | 70.7 (61.9–79.6)*             | 70.7 (61.9–79.6)* | <0.01|
| TG, mM           | 0.73 (0.57–0.99)  | 1.07 (0.73–1.45)*           | 1.12 (0.80–1.61)*             | 1.62 (1.12–2.31)* | <0.01|
| HDL-C, mM        | 1.86 (1.61–2.15)  | 1.58 (1.35–1.92)*           | 1.58 (1.32–1.86)*             | 1.35 (1.17–1.61)* | <0.01|
| Periodic exercise,a, n | 1487 (30.2%)    | 78 (28.9%)                  | 818 (34.4%)                   | 515 (27.4%)       | <0.01|
| Snacking habits,b, n | 3507 (71.1%)   | 168 (62.0%)                 | 1454 (61.2%)                  | 1091 (58.0%)      | <0.01|
| Drinker,c, n     | 317 (6.4%)        | 22 (8.1%)                   | 238 (10.0%)                   | 175 (9.3%)        | <0.01|
| Current smoker, n | 767 (15.6%)       | 57 (21.0%)                  | 645 (27.1%)                   | 570 (30.3%)       | <0.01|
| Family history of diabetes, n | 964 (19.6%) | 56 (20.7%)                 | 439 (18.5%)                   | 391 (20.8%)       | 0.28|
| Onset of diabetes mellitus,d, n | 25 (0.5%)   | 5 (1.8%)                    | 60 (2.52%)                    | 139 (7.36%)       | <0.01|

Data are presented as median (interquartile range) or number (percentage). The Steel-Dwass test and χ² test were used to analyze continuous and categorical variables, respectively. Differences were considered significant at P < 0.05 (*normal vs simple fatty liver, †normal vs metabolic disorder, §normal vs MAFLD, ¶simple fatty liver vs metabolic disorder, ¤simple fatty liver vs MAFLD, ¦metabolic disorder vs MAFLD). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cre, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides. aExercise habit: no habit or awareness of exercise vs periodic exercise. bSnacking habit: no snacking vs snacking ≥1 time/day. cDrinker: men: ≥210 g/week; women: ≥140 g/week. dDM onset was defined as fasting glucose levels ≥6.99 mM, HbA1c ≥6.5%, or initiation of anti-diabetes treatment.
The comparisons of characteristics between baseline and endpoint revealed that BMI, DBP, and AST levels at endpoint were higher than at baseline among the normal, simple fatty liver, and metabolic disorder groups (Table 3). The FPG levels at endpoint were higher than at baseline, and HDL-c levels at endpoint were lower than at baseline among all groups and the proportion of current smokers was lower at endpoint than at baseline among normal, metabolic disorder, and MAFLD groups (Table 3). The proportion of individuals with periodic exercise habits was higher at endpoint than at baseline among all groups and the proportion of current smokers was lower at endpoint than at baseline among normal, metabolic disorder, and MAFLD groups (Table 3).

**Risk of DM onset with simple fatty liver, metabolic disorder, and MAFLD**

Univariate analysis revealed that simple fatty liver, metabolic disorder, and MAFLD were significant risk factors for DM compared with the normal group. Further, MAFLD had a higher risk of DM onset than simple fatty liver and metabolic disorder (simple fatty liver, HR: 3.61, 95% CI: 1.38-9.43; metabolic disorder, HR: 5.41, 95% CI: 3.39-8.62; MAFLD, HR: 18.46, 95% CI: 12.06-28.27) (P-trend <0.01; Table 4). In addition, multivariate analysis adjusted for sex, age, BMI, Cre, exercise habit, snacking habit, drinking habit, smoking habit, family history of diabetes, and metabolic disorder, including overweight/obesity, hypertension, high TG levels, low HDL-c levels, or pre-diabetes, showed a significantly increased risk of DM onset in the other three groups compared with the normal group (simple fatty liver, aHR: 2.76, 95% CI: 1.05-7.23; metabolic disorder, aHR: 3.62, 95% CI: 2.24-5.85; MAFLD, aHR: 11.03, 95% CI: 7.03-17.28) (P-trend <0.01; Table 4).

In the normal, simple fatty liver, metabolic disorder, and MAFLD groups, the 1-year DM onset rates were 0.04%, 0%, 0.03%, and 0.5%, respectively; the 3-year DM onset rates were 0.11%, 0.43%, 1.06%, and 3.15%, respectively; the 5-year DM onset rates were 0.44%, 1.64%, 2.07%, and 5.37%, respectively; and the 10-year DM onset rates were 0.69%, 3.72%, 5.25%, and 16.68%, respectively.

**Risk of fatty liver disease combined with other factors**

Next, we examined the factors that exacerbated the risk of fatty liver disease in DM. Fatty liver disease with overweight/obesity or pre-diabetes significantly increased the risk of DM onset compared with fatty liver disease with other metabolic diseases (overweight/obesity, HR: 3.21, 95% CI: 1.75-5.94; pre-diabetes, HR: 8.54, 95% CI: 4.92-14.82, respectively; Table 5). Additionally, multivariate analysis adjusted for sex; age; BMI; Cre levels; exercise habit; snacking habit; drinking habit; smoking habit; family history of diabetes; and metabolic disorders, including overweight/obesity, hypertension, high TG levels, low HDL-c levels, or pre-diabetes, showed a significantly increased risk of DM onset in fatty liver disease with overweight/obesity and pre-diabetes (overweight/obesity, HR: 2.18, 95% CI: 1.15-4.13; pre-diabetes, HR: 7.82, 95% CI: 4.37-13.99, respectively; Table 5). In the fatty liver with overweight/obesity and pre-diabetes groups, the 1-year DM onset rates were 0.54 and 0.07%, respectively; the 3-year DM onset rates were 3.28 and 4.65%, respectively; the 5-year DM onset rates were 5.53 and 7.89%, respectively; and the 10-year DM onset rates were 16.99 and 24.1%, respectively.
Table 3 | The differences in characteristics between baseline and endpoint

| Group                           | Normal (n = 4,930) | Simple fatty liver (n = 271) | Metabolic disorder (n = 2,377) | MAFLD (n = 1,881) |
|---------------------------------|--------------------|-----------------------------|-----------------------------|------------------|
| **BMI, kg/m²**                  | 20.4 (19–21.5)    | 20.6 (19.3–22)              | 21.9 (20.7–22.8)            | 24.1 (23.2–25.5) |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **SBP, mmHg**                   | 105 (97–114)      | 105 (96–115)                | 111 (101–119)              | 118 (108–132)    |
|                                 | 0.94               | 0.09                        | 0.09                        | 0.09             |
| **DBP, mmHg**                   | 65 (59–72)        | 66 (59–73)                  | 70 (64–76)                 | 74 (66–84)       |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **FPG, mM**                     | 4.94 (4.66–5.16)  | 4.94 (4.72–5.22)            | 5.16 (4.88–5.44)           | 5.22 (4.94–5.55) |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **HbA1c, %**                    | 5.4 (5.1–5.6)     | 5.4 (5.2–5.5)               | 5.5 (5.2–5.6)              | 5.5 (5.2–5.7)    |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **AST, IU/L**                   | 19 (16–22)        | 19 (17–23)                  | 22 (18–26)                 | 24 (19–26)       |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **ALT, IU/L**                   | 14 (12–19)        | 15 (12–19)                  | 21 (14–30)                 | 19 (14–26)       |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **Cre, µM**                     | 61.9 (53.0–70.7)  | 61.9 (53.0–70.7)            | 67.2 (64.8–77.8)           | 70.7 (61.9–79.6) |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **TG, mM**                      | 1.86 (1.61–2.15)  | 1.74 (1.50–2.02)            | 1.48 (1.27–1.76)           | 1.48 (1.27–1.76) |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **Periodic exercise, n**        | 1487 (30.2%)      | 1823 (37.0%)                | 101 (37.3%)                | 1017 (42.8%)     |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |
| **Snacking habits, n**          | 3507 (71.1%)      | 3539 (71.8%)                | 175 (64.6%)                | 1435 (61.2%)     |
|                                 | 0.48               | 0.53                        | 0.53                        | 0.53             |
| **Drinker, n**                  | 317 (6.4%)        | 35 (7.9%)                   | 28 (8.9%)                  | 24 (8.9%)       |
|                                 | 0.06               | 0.86                        | 0.26                        | 0.26             |
| **Current smoker, n**           | 767 (15.6%)       | 645 (13.1%)                 | 48 (17.7%)                 | 645 (27.1%)     |
|                                 | <0.01             | <0.01                       | <0.01                       | <0.01            |

The Wilcoxon signed rank test and χ² test were used to analyze continuous and categorical variables, respectively. Differences were considered significant at P < 0.05. Data are presented as median (interquartile range) or number (percentage). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cre, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides. Exercise habit: no habit or awareness of exercise vs periodic exercise. Snacking habit: no snacking vs snacking ≥1 time/day. Drinker: men: ≥210 g/week, women: ≥140 g/week.
Table 4 | The risk for the onset of diabetes mellitus

|                      | Normal          | Simple fatty liver | Metabolic disorder | MAFLD            | P for trend |
|----------------------|-----------------|-------------------|-------------------|------------------|------------|
| Crude HR (95% CI)    | 1.00 (1.00–1.00)| 3.61 (3.38–3.84)  | 5.41 (3.39–8.62)  | 18.46 (12.06–28.27) | <0.01      |
| Adjusted HR† (95% CI)| 1.00 (1.00–1.00)| 2.76 (1.05–7.23)  | 3.62 (2.24–5.85)  | 11.03 (7.03–17.28) | <0.01      |

Differences were considered statistically significant for \( P < 0.05 \). BMI, body mass index; CI, confidence interval; Cre, creatinine; HR, hazard ratio; SBP, systolic blood pressure. †Multivariate Cox proportional hazards regression analysis was adjusted for sex, age (years), BMI (kg/m²), SBP (mmHg), Cre (µM), exercise habits, snacking habits, drinking habits, smoking status, and family history of diabetes.

Table 5 | Risk of fatty liver in combination with other factors

|                      | Crude HR (95% CI) | P-value | Adjusted HR† (95% CI) | P-value |
|----------------------|-------------------|---------|-----------------------|---------|
| Overweight/obese     | 3.21 (1.73–5.94)  | <0.01   | 2.18 (1.15–4.13)      | 0.02†   |
| Hypertension         | 1.77 (1.28–2.46)  | <0.01   | 1.18 (0.83–1.69)      | 0.35†   |
| High TG level        | 1.85 (1.33–2.58)  | <0.01   | 1.25 (0.86–1.81)      | 0.24†   |
| Low HDL-C level      | 1.41 (0.91–2.20)  | 0.13    |                       |         |
| Pre-diabetes         | 8.54 (4.92–14.82) | <0.01   | 7.82 (4.37–13.99)     | <0.01‡  |

Differences were considered statistically significant for \( P < 0.05 \). BMI, body mass index; CI, confidence interval; Cre, creatinine; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SBP, systolic blood pressure; TG, triglycerides. †Multivariate Cox proportional hazards regression analysis was adjusted for sex, age (years), BMI (kg/m²), SBP (mmHg), Cre (µM), exercise habits, snacking habits, drinking habits, smoking status, and family history of diabetes, along with metabolic disorders as follows: hypertension, high TG levels, low HDL-C levels, and pre-diabetes; ‡overweight/obese, high TG levels, low HDL-C levels, and pre-diabetes; ‡overweight/obese, hypertension, low HDL-C levels, and pre-diabetes; †overweight/obese, hypertension, high TG levels, and low HDL-C levels.

DISCUSSION

We observed that fatty liver with metabolic disorders, such as MAFLD, indicated an increased risk of DM onset compared with simple fatty liver and metabolic disorders. Additionally, fatty liver disease in the presence of overweight/obesity or pre-diabetes showed a higher risk of DM onset compared with fatty liver disease with other metabolic disorders. Therefore, MAFLD, especially fatty liver disease with overweight/obesity or pre-diabetes, is an appropriate disease concept for the risk of DM development.

Nonalcoholic fatty liver disease is a significant risk factor for DM; moreover, NAFLD is strongly associated with DM. Additionally, a previous examination of the relationship between the changes in fatty liver status over time and the risk of DM onset indicated that, although improvement of fatty liver did not reduce the risk of developing DM as low as that in non-fatty liver patients, exacerbation of the severity of fatty liver disease notably increased the risk of DM onset. Therefore, it is important to intervene in cases of fatty liver disease to reduce the risk of DM onset. However, since NAFLD is diagnosed after excluding other liver diseases, it is difficult to properly evaluate various diseases that could complicate NAFLD pathogenesis, including viral hepatitis, alcoholic liver disease, and autoimmune liver diseases. In 2020, the concept of MAFLD was proposed, which facilitated the pathogenesis of fatty liver disease. Although we included 128 patients with HBs-Ag, 91 patients with anti-HCV, and 752 drinkers, the relationship between fatty liver disease and diabetes could be accurately represented. Additionally, MAFLD is a good predictive factor of hepatic fibrosis and mortality. There is a need for future studies on MAFLD to confirm whether MAFLD is carries increased risk factors for other diseases.

Our findings confirmed that fatty liver disease was classified according to the risk of DM. Liang et al. reported that compared with participants without fatty liver disease, patients with MAFLD and NAFLD had an increased risk of DM onset (estimated risk ratio [RR] 2.08, 95% CI 1.72–2.52; RR 2.01, 95% CI 1.65–2.46, respectively) after adjustment for age, sex, educational background, smoking status, and leisure-time exercise. Moreover, the change from NAFLD to MAFLD had no effect on the relationship with diabetes. However, since this previous study compared disease concepts, there was an overlap in the target participants with NAFLD and MAFLD. Therefore, our findings are important since we stratified participants based on their risk of DM development, and they demonstrated that a diagnosis of MAFLD can be used to identify patients at a higher risk of developing DM. Additionally, we analyzed the factors that specifically increased the risk of fatty liver disease.

Our study strengths are that only five data points were missing from the entire cohort of patients and visits (one BMI measurement, and two points each for exercise and snacking habits). However, this study has several limitations. First, because we did not collect data pertaining to waist circumference, insulin levels, or high-sensitivity C-reactive protein levels, we could not assess all the MAFLD components. Therefore, it is possible that the number of patients with MAFLD was
underestimated. Second, although abdominal ultrasonography is a reliable diagnostic method with high sensitivity and specificity for fatty liver disease, we could not assess the effects of the severity of fatty liver disease on DM development since we could not determine the extent of fatty liver disease and fibrosis. Third, self-reported data were used for some of the factors surveyed, which may compromise the accuracy of the survey results. Fourth, the data are not truly continuous because they were collected only once a year at annual health check-ups. Fifth, it is possible that some of the participants who developed DM after the health check-up missed the next health check-up. Therefore, the number of patients who developed diabetes may have been underestimated. Finally, since we only studied the Japanese population, studies with other populations are needed to confirm the generality of our results.

In conclusion, our findings demonstrated that a diagnosis of MAFLD can be used to classify a high risk of DM onset among patients with fatty liver disease. Additionally, among patients with fatty liver disease, those with fatty liver who are also overweight/obese or have pre-diabetes are at a higher risk of developing DM. Therefore, clinicians should be particularly vigilant when treating patients with fatty liver complicated by metabolic disorders, such as MAFLD, to prevent the development of DM. Stratifying the risk of fatty liver can allow the identification of, and interventions for, patients at a high risk of diabetes development.

ACKNOWLEDGMENTS
This study was supported by a research grant from JSPS KAKENHI (JP19K11743). We are grateful to Editage (www.editage.com) for providing English language editing.

DISCLOSURE
The authors declare that they have no conflicts of interest. Approval of the research protocol: This study was approved by the Research Ethics Committee of Ehime University Hospital (approval number: 1709007). Informed consent: N/A. Since this study protocol was retrospective in manner and all the participants’ data were de-identified, it was not necessary to obtain informed consent from participants in this study. Registry and the registration no. of the study/trial: October 3, 2013 University Hospital Medical Information Network ID: UMIN000011953. Animal studies: N/A.

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