Independent Association Between Improvement of Nonalcoholic Fatty Liver Disease and Reduced Incidence of Type 2 Diabetes

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OBJECTIVE

Only a few studies have evaluated the long-term effects of nonalcoholic fatty liver disease (NAFLD) on type 2 diabetes mellitus (T2DM), and none have examined whether NAFLD improvement reduces T2DM incidence. We investigated the association between NAFLD improvement and T2DM incidence.

RESEARCH DESIGN AND METHODS

Between 2000 and 2012, 4,604 participants who underwent a health check twice with >10 years between were enrolled. Exclusion criteria were positive hepatitis B surface antigen, positive hepatitis C antibody, ethanol intake >20 g/day, and diabetes. The 3,074 eligible participants were divided into an NAFLD group (*n* = 728) and a non-NAFLD group (*n* = 2,346) according to ultrasonography-detected fatty liver. The NAFLD group was categorized into an improved group (*n* = 110) and a sustained NAFLD group (*n* = 618) based on fatty liver disappearance at the second visit. Incident T2DM odds ratios (ORs) were estimated by logistic regression models adjusted for age, sex, BMI, impaired fasting glucose, family history of diabetes, dyslipidemia, hypertension, and physical exercise.

RESULTS

T2DM occurred in 117 participants (16.1%) in the NAFLD group and 72 (3.1%) in the non-NAFLD group. NAFLD at baseline was associated with T2DM incidence (multivariate OR 2.37 [95% CI 1.60–3.52]). T2DM occurred in 7 participants (6.4%) in the improved group and in 110 (17.8%) in the sustained NAFLD group. NAFLD improvement was associated with reduced T2DM incidence (multivariate OR 0.27 [95% CI 0.12–0.61]).

CONCLUSIONS

NAFLD improvement is associated with T2DM incidence reduction.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver function tests in many countries. Dietary habits and lifestyles have dramatically changed in recent decades, and NAFLD has become a worldwide public health problem (1–3). NAFLD is associated with not only hepatic complications such as liver cirrhosis and hepatocellular carcinoma but also extrahepatic complications, including metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) (3). NAFLD is a multisystem disease that requires a multidisciplinary approach to management (1,3). In fact, the most common cause of death in patients

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with NAFLD is CVD. Therefore, evaluating the associated metabolic disturbances, including T2DM, to reduce CVD in patients with NAFLD is important (4).

NAFLD is not only a liver manifestation of current metabolic syndrome but also a risk factor for future metabolic syndrome, T2DM, and CVD (1–5). Lonardo et al. (2) showed in a systematic review that NAFLD is strongly associated with future metabolic syndrome and T2DM. In addition, several longitudinal studies evaluated the association between NAFLD detected on ultrasound (US) and T2DM (6–14). Most of these studies observed a significant positive association between NAFLD at baseline and T2DM incidence (6–13), but long-term cohort studies with a follow-up period of >10 years are limited (14).

To our knowledge, the association between NAFLD improvement and T2DM incidence reduction remains unknown. NAFLD treatment is expected to have a preventive effect on T2DM because NAFLD is a strong determinant of T2DM incidence (1–5). Sung et al. (15) reported that resolution of fatty liver is not associated with increased T2DM incidence. However, their study focused on fatty liver not on NAFLD, because they did not exclude causes of secondary hepatic fat accumulation, such as chronic viral hepatitis and excessive alcohol consumption. Therefore, a study focusing on NAFLD is needed. Of note, NAFLD can be improved by lifestyle modifications such as dietary restriction and increased physical activity (16–20). Thus, the risk of T2DM can be speculated to be lower in patients with improved NAFLD than in those with sustained NAFLD because the effects of NAFLD on T2DM could be attenuated by diminished hepatic steatosis. Because NAFLD is considered a risk factor for T2DM (1–13), the next clinical issue to address is whether NAFLD improvement is associated with T2DM incidence reduction.

In this 10-year cohort study, we investigated the association between NAFLD improvement and T2DM incidence reduction. We also evaluated the long-term effects of NAFLD on T2DM incidence.

RESEARCH DESIGN AND METHODS

Subjects

This retrospective cohort study was conducted to assess the long-term effects of NAFLD on T2DM incidence in Keijinkai Maruyama Clinic, Sapporo, Japan. A total of 4,604 participants received an abdominal US health check twice between 2000 and 2012, with an interval of >10 years between the health checks. Among the 4,604 participants, 3,074 were eligible for this study after exclusion by a positive serologic marker for hepatitis B surface antigen (*n* = 189), a positive serologic marker for hepatitis C antibody (*n* = 35), ethanol intake >20 g/day (*n* = 1,246), and diabetes at baseline (*n* = 204). Some participants met more than one exclusion criterion. The 3,074 eligible participants were divided into an NAFLD group (*n* = 728) and a non-NAFLD group (*n* = 2,346) according to US-detected fatty liver at the time of the first examination. The NAFLD group was further categorized into an improved group (*n* = 110) and a sustained NAFLD group (*n* = 618) based on fatty liver disappearance at the second health check. The participants in the improved group were diagnosed as having NAFLD at baseline but not at the second visit. The mean ± SD interval between the health checks was 11.3 ± 0.8 years. The study flow diagram is shown in Fig. 1.

NAFLD Diagnosis

Participants with fatty liver were regarded as those with NAFLD after exclusion of hepatitis B, hepatitis C, and ethanol intake >20 g/day. Fatty liver was diagnosed using US (SSA-340A and SSA-325A with a 3.75-MHz convex probe at baseline, SSA-680A and TUS-A400 with a 3.5-MHz convex probe at the second visit; Toshiba, Otawara, Japan). Standard US criteria for fatty liver were applied; fatty liver was ascertained by the discrepancy of echo amplitude between the liver and the kidney with increased liver echogenicity (21). Abdominal US was performed by experienced technicians who had no knowledge of the study objective. US images were captured with an instant film and inspected by physicians who had no knowledge of the study.

T2DM Incidence

We regarded the study participants who met any of the following four factors as having T2DM: fasting plasma glucose ≥126 mg/dL, hemoglobin A_{1c} ≥6.5% (48 mmol/mol), self-reported physician-diagnosed diabetes, or taking any medication for diabetes. T2DM incidence was compared between the NAFLD group and the non-NAFLD group to assess whether NAFLD was a significant risk factor for T2DM. To evaluate the association between NAFLD improvement and T2DM risk reduction, the improved group was compared with the sustained NAFLD group in terms of T2DM incidence.

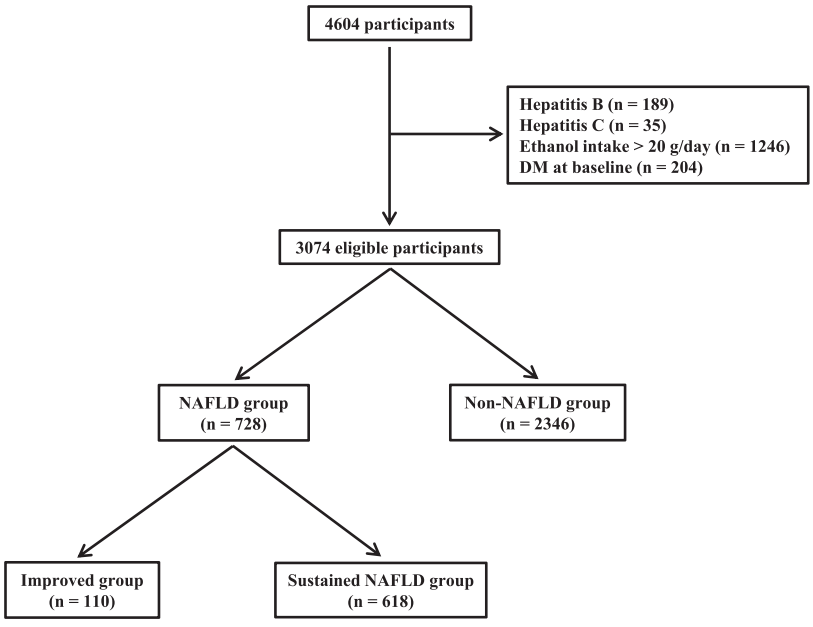

Figure 1—Study flow diagram. Some participants met more than one exclusion criterion. The participants in the improved group were diagnosed as having NAFLD at baseline but not at the second health check. On the other hand, the participants in the sustained NAFLD group had NAFLD at both baseline and the second health check. DM, diabetes mellitus.

Covariates

All participants filled out questionnaires about smoking cigarettes, alcohol drinking habits, medical history, medications, family history of diabetes, and physical exercise. Questions on alcohol drinking habits included the amount and frequency of alcohol consumption. We defined participants who answered "I don't drink alcohol" as never-drinkers. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Dyslipidemia (DL) was diagnosed when the participants met any of the following four factors: high triglycerides level (≥150 mg/dL), low HDL cholesterol level (<40 mg/dL), high LDL cholesterol level (≥140 mg/dL), or self-reported physician-diagnosed DL. Hypertension (HT) was confirmed when either of the following two factors was met: elevated systolic or diastolic blood pressure (≥140/90 mmHg) or self-reported physician-diagnosed HT. Impaired fasting glucose (IFG) was diagnosed when the fasting plasma glucose level was between 100 and 125 mg/dL. Participants who engaged in physical exercise more than twice a week were categorized as physically active.

Statistical Analysis

Data on baseline characteristics are expressed as mean ± SD. Logistic regression models were used to estimate the crude odds ratios (ORs), multivariate adjusted ORs, and 95% CIs for the association between NAFLD at baseline and T2DM incidence as well as between NAFLD improvement and T2DM incidence. On the multivariate analysis, age, sex, BMI, IFG, family history of diabetes, DL, HT, and physical exercise were adjusted as potential confounders between NAFLD and T2DM. Stratified analysis by sex was conducted because NAFLD is more prevalent in men than in women (22–26), and its pathogenesis has a sex-related difference (22,26).

We repeated the analysis with restricted participants to exclude the effects of alcohol consumption among *1*) never-drinkers and *2*) participants whose γ-glutamyltransferase (GGT) level was <100 units/L. Although alcoholic fatty liver disease and NAFLD might be considered the same disease with different etiologies (27), differentiating them in terms of their prevention and management is important. Despite its limitation as an indicator of alcohol consumption, GGT was selected as a commonly used marker (6) because of the lack of a widely available and reliable biomarker (28). When the association between NAFLD improvement and T2DM incidence was assessed, stratified analysis by BMI change between the first and second health checks was added.

$P < 0.05$ was considered to indicate a statistically significant difference. SAS 9.3 software (SAS Institute, Cary, NC) was used for all statistical analyses. Dummy variables were used for missing data, with the creation of a categorical indicator for missing responses (missing category).

Ethical Considerations

This study was approved by the ethics committee of Teine Keijinkai Hospital. The informed consent requirement was waived because this research used a retrospective study design.

RESULTS

Baseline Characteristics

Participant baseline data are shown in Table 1. The NAFLD prevalence was 23.7% (728 of 3,074) at baseline. In the NAFLD group, the proportion of men was 83.9% (611 of 728), and the mean BMI was 26.0 ± 2.9 kg/m^2. The prevalence proportions of DL and HT in the NAFLD group were 65.9% (480 of 728) and 19.9% (145 of 728), respectively.

Association Between NAFLD at Baseline and T2DM Incidence

The overall incidence of T2DM was 6.1% (189 of 3,074) during the follow-up. The incidence varied substantially, depending on the NAFLD condition at baseline (16.1% [117 of 728] in the NAFLD group, 3.1% [72 of 2,346] in the non-NAFLD group). Table 2 shows the ORs and 95% CIs for the association between NAFLD at baseline and T2DM incidence. The crude OR was 6.05 (95% CI 4.45–8.22). After adjusting for age, sex, BMI, IFG, family history of diabetes, DL, HT, and

Table 1—Baseline characteristics of participants in the NAFLD and non-NAFLD groups

	NAFLD group (*n* = 728)	Non-NAFLD group (*n* = 2,346)
Age (years)	43.8 ± 7.3	43.0 ± 7.2
Male:female sex	611:117	1,255:1,091
BMI (kg/m^2)	26.0 ± 2.9	21.8 ± 2.5
Aspartate aminotransferase (units/L)	27.7 ± 11.9	20.3 ± 5.7
Alanine aminotransferase (units/L)	40.7 ± 24.3	20.0 ± 10.9
GGT (units/L)	66.8 ± 71.5	33.6 ± 35.7
Bilirubin (mg/dL)	0.77 ± 0.35	0.75 ± 0.32
Albumin (g/dL)	4.4 ± 0.2	4.3 ± 0.2
Platelet count (× 10^9/L)	231 ± 50	225 ± 48
Fasting plasma glucose (mg/dL)	99.1 ± 9.3	94.0 ± 8.6
HbA_{1c} (%)	5.3 ± 0.3	5.1 ± 0.3
HbA_{1c} (mmol/mol)	34 ± 3.3	32 ± 3.3
IFG	336 (46.1)	533 (22.7)
Family history of diabetes	127 (17.4)	320 (13.6)
DL	480 (65.9)	619 (26.4)
Triglycerides (mg/dL)	146.1 ± 126.1	87.0 ± 50.9
HDL cholesterol (mg/dL)	50.3 ± 11.1	61.5 ± 15.0
LDL cholesterol (mg/dL)	136.0 ± 30.7	116.6 ± 27.7
Lipid-lowering drug	30 (4.1)	29 (1.2)
HT	145 (19.9)	196 (8.4)
Systolic blood pressure (mmHg)	122.4 ± 13.3	115.6 ± 14.0
Diastolic blood pressure (mmHg)	80.2 ± 9.8	74.6 ± 10.2
Antihypertensive drug	41 (5.6)	56 (2.4)
Current smoker	270 (40.4)	750 (34.7)
Physical exercise	81 (11.1)	377 (16.1)

Data are mean ± SD or *n* (%) unless otherwise indicated.

Table 2—ORs and 95% CIs for the association between NAFLD at baseline and T2DM incidence, stratified by sex

	All participants (n = 3,074)				Men (n = 1,866)		Women (n = 1,208)	
	Crude		Multivariate adjusted		Multivariate adjusted		Multivariate adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
NAFLD at baseline	6.05 (4.45–8.22)	<0.001	2.37 (1.60–3.52)	<0.001	2.27 (1.47–3.51)	<0.001	3.01 (1.18–7.68)	0.021
Age (continuous)	—	—	1.04 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.0022	1.05 (1.00–1.11)	0.073
Women	—	—	0.91 (0.61–1.35)	0.63	—	—	—	—
BMI (continuous)	—	—	1.11 (1.04–1.17)	0.0010	1.12 (1.04–1.20)	0.0017	1.05 (0.94–1.18)	0.37
IFG	—	—	4.11 (2.93–5.77)	<0.001	3.62 (2.47–5.32)	<0.001	6.12 (3.09–12.14)	<0.001
Family history of diabetes	—	—	2.16 (1.50–3.13)	<0.001	2.03 (1.32–3.13)	0.0013	2.76 (1.33–5.78)	0.0066
DL	—	—	1.68 (1.18–2.39)	0.0040	1.73 (1.15–2.59)	0.0084	1.45 (0.68–3.11)	0.34
HT	—	—	1.08 (0.71–1.63)	0.73	1.06 (0.67–1.67)	0.81	1.16 (0.43–3.08)	0.77
Physical exercise	—	—	0.54 (0.31–0.95)	0.034	0.55 (0.28–1.06)	0.074	0.47 (0.15–1.51)	0.21

Logistic regression models were used to estimate the ORs, 95% CIs, and P values.

physical exercise, the multivariate adjusted OR was 2.37 (95% CI 1.60–3.52).

Stratified analysis by sex was also conducted (Table 2). The T2DM incidences were 7.9% (148 of 1,866) in men and 3.4% (41 of 1,208) in women. The T2DM incidences were 16.4% (100 of 611) and 3.8% (48 of 1,255) in men with and without NAFLD, respectively, and 14.5% (17 of 117) and 2.2% (24 of 1,091) in women with and without NAFLD, respectively. After adjusting for age, BMI, IFG, family history of diabetes, DL, HT, and physical exercise, the multivariate adjusted ORs were 2.27 (95% CI 1.47–3.51) in men and 3.01 (95% CI 1.18–7.68) in women. NAFLD was significantly associated with T2DM incidence in women and men.

Subgroup analyses among never-drinkers only (n = 1,156) and among participants with GGT <100 units/L only (n = 2,878) were conducted. The incidences of T2DM were 6.5% (75 of 1,156) in never-drinkers and 5.6% (160 of 2,878) in participants with GGT <100 units/L. After adjusting for age, sex, IFG, BMI, family history of diabetes, DL, HT, and physical exercise, the multivariate adjusted ORs were 2.12 (95% CI 1.08–4.15) and 2.43 (1.58–3.75) in never-drinkers and participants with GGT <100 units/L, respectively. The results from the subgroup analyses were consistent with the overall results.

Association Between NAFLD Improvement and T2DM Incidence

The improvement rate of NAFLD during the follow-up was 15.1% (110 of 728), and the T2DM incidences were 6.4% (7 of 110) and 17.8% (110 of 618) in the improved and sustained NAFLD groups, respectively. Table 3 shows the ORs and 95% CIs for the association between NAFLD improvement and T2DM incidence. The crude OR was 0.31 (95% CI 0.14–0.69). After adjusting for age, sex, BMI, IFG, family history of diabetes, DL, HT, and physical exercise, the multivariate adjusted OR was 0.27 (95% CI 0.12–0.61). NAFLD improvement was associated with reduced T2DM incidence.

Stratified analysis by BMI change between the first and second health checks was also conducted (Table 3). The T2DM incidences were 14.4% (63 of 438) and 18.6% (54 of 290) in participants with a BMI increase and BMI decrease, respectively. There were no participants without a BMI change. After adjusting for age, sex, BMI, IFG, family history of diabetes, DL, HT, and physical exercise, the multivariate adjusted ORs were 0.40 (95% CI 0.051–3.10) in participants with a BMI increase and 0.18 (0.069–0.46) in those with a

Table 3—ORs and 95% CIs for the association between NAFLD improvement and T2DM incidence among participants with NAFLD at the first examination, stratified by BMI change

	Participants with NAFLD at baseline (n = 728)				BMI increase (n = 438)		BMI decrease (n = 290)	
	Crude		Multivariate adjusted		Multivariate adjusted		Multivariate adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
NAFLD improvement	0.31 (0.14–0.69)	0.0042	0.27 (0.12–0.61)	0.0017	0.40 (0.051–3.10)	0.38	0.18 (0.069–0.46)	<0.001
Age (continuous)*	—	—	1.03 (1.00–1.07)	0.040	1.06 (1.02–1.11)	0.0053	1.00 (0.95–1.05)	0.91
Women*	—	—	1.00 (0.54–1.87)	1.00	1.15 (0.50–2.61)	0.74	0.71 (0.25–1.98)	0.51
BMI (continuous)*	—	—	1.06 (0.98–1.15)	0.13	1.07 (0.97–1.18)	0.19	1.05 (0.93–1.19)	0.46
IFG*	—	—	3.25 (2.08–5.07)	<0.001	2.24 (1.25–4.01)	0.0069	6.21 (2.84–13.58)	<0.001
Family history of diabetes*	—	—	2.28 (1.40–3.71)	0.0010	2.19 (1.13–4.26)	0.021	2.27 (1.05–4.92)	0.038
DL*	—	—	1.77 (1.08–2.89)	0.024	2.06 (1.04–4.07)	0.038	1.63 (0.77–3.45)	0.20
HT*	—	—	0.99 (0.59–1.65)	0.96	1.14 (0.59–2.20)	0.71	0.79 (0.33–1.88)	0.59
Physical exercise*	—	—	0.92 (0.44–1.93)	0.82	0.90 (0.32–2.51)	0.84	1.38 (0.44–4.34)	0.58
Physical exercise at follow-up	—	—	0.64 (0.36–1.16)	0.14	0.73 (0.31–1.70)	0.46	0.48 (0.20–1.11)	0.087

Logistic regression models were used to estimate the ORs, 95% CIs, and P values. NAFLD improvement was defined as NAFLD at baseline but not at the second health check. BMI change means change in BMI between the first and second health checks. *These characteristics were based on information at baseline.

BMI decrease. NAFLD improvement was significantly associated with T2DM incidence reduction among participants with a BMI decrease.

CONCLUSIONS

This retrospective 10-year follow-up study of a cohort of 3,074 eligible participants revealed that US-detected NAFLD at baseline was associated with T2DM incidence. Of note, NAFLD improvement was significantly associated with a lower T2DM incidence after adjusting for potential confounders (i.e., age, sex, BMI, IFG, family history of diabetes, DL, HT, physical exercise). The positive association between NAFLD at baseline and T2DM incidence is consistent with that of previous studies (6–13) but not with the 10-year longitudinal study by Okamoto et al. (14), which showed no significant association between NAFLD and T2DM (OR 1.85 [95% CI 0.40–8.51]). The discrepancy between Okamoto et al. and the current study could be explained by the false-negative error in Okamoto et al.; the ratio of T2DM incidence/participants in their study was 20/136, whereas that in the current study was 189/3,074 (14). The present 10-year cohort study involving a large number of participants revealed that NAFLD is a significant risk factor for T2DM over the long term.

Women are less likely to have NAFLD than men, possibly because of female hormones. This speculation is supported by previous studies showing that hormone replacement therapy reduces the risk for NAFLD in postmenopausal women (22,24). In addition, Bae et al. (23) reported that 40.2% of men and 10.3% of women had NAFLD. We also confirmed in this study that the prevalence of NAFLD at baseline was lower in women (9.7%) than in men (32.7%). A previous population-based prospective study reported a T2DM incidence in 10 years of 5.4% in men and 3.0% in women (29), and the sex difference in T2DM incidence was similar to that in the present study (7.9% in men, 3.4% in women). The current study revealed that NAFLD at baseline increased the risk of T2DM incidence in both women and men independent of potential confounders (i.e., age, BMI, IFG, family history of diabetes, DL, HT, physical exercise). Both NAFLD and T2DM are less common in women than in men, and T2DM might be induced by NAFLD regardless of sex. Therefore, we speculate that sex difference in T2DM incidence might be substantially explained by the dissociation of NAFLD prevalence between men and women. Thus, NAFLD prevention might be important to reduce T2DM incidence in both women and men.

The current study showed a positive association between NAFLD improvement and T2DM incidence reduction independent of the potential confounders. The possible explanations are that *1*) NAFLD improvement reduced T2DM incidence and *2*) other factors (e.g., lifestyle modification) affected both NAFLD improvement and T2DM risk reduction. Exercise and diet modification were previously shown to improve hepatic steatosis (30,31) and normalize altered liver tests (32). Lifestyle intervention also reduced the risk of T2DM (33). Therefore, it is reasonable to speculate that lifestyle modification affects both NAFLD improvement and T2DM incidence reduction. However, the possibility that NAFLD improvement also decreased T2DM incidence cannot be disregarded. Because this study showed that NAFLD is an independent risk factor for T2DM after adjustment for potential confounders, NAFLD improvement may reduce T2DM incidence. In fact, Ogata et al. (34) reported that NAFLD improvement is associated with improvement of impaired glucose tolerance to normal glucose regulation. NAFLD improvement thus may lead to recovery from impaired glucose tolerance (34). Further studies are needed to validate the causal relationship between NAFLD improvement and T2DM incidence reduction.

Insulin resistance (IR) has been shown in clinical studies to be strongly associated with NAFLD (23,35) and thus plays a key role in the association of NAFLD with T2DM. Although the underlying mechanism is not fully understood, NAFLD may cause T2DM by increasing IR. Hepatokines have been found to be associated with IR, and this might partly explain the mechanism of how NAFLD causes T2DM (1). Unfortunately, we do not have data on fasting insulin and hepatokines to allow us to specifically elucidate the mechanism linking improved NAFLD to protection from T2DM development. Further research is necessary to clarify the exact mechanism of how NAFLD causes T2DM.

NAFLD is a risk factor not only for T2DM but also for metabolic syndrome and CVD (2,36,37). In their systematic review, Lonardo et al. (2) found that NAFLD is a major risk factor for metabolic syndrome. Moreover, CVD is the main cause of death in patients with NAFLD (4), and NAFLD is a strong determinant of CVD (37). In the current study, we show the independent association between NAFLD improvement and T2DM incidence reduction; thus, we expect that NAFLD improvement also has preventive effects on metabolic syndrome and CVD. In particular, CVD is directly associated with mortality. Therefore, future studies should evaluate whether NAFLD improvement reduces CVD events and mortality in patients with NAFLD.

This study has several limitations. First, the participants voluntarily underwent a health check twice and may be healthier and more health conscious than the general population. A previous Japanese multicenter study showed an NAFLD prevalence of 29.7% (38), which was not substantially different from the current study's NAFLD prevalence of 23.7%. The T2DM incidence of 4.1% from a previous Japanese 10-year population-based study (29) was not substantially different from the current study's T2DM incidence of 6.1%. Therefore, the present participants are considered as representative of the general Japanese population in terms of NAFLD and T2DM. Second, NAFLD was not confirmed by biopsy specimen but was detected by US. The presence of hepatic steatosis is underestimated on US when there is $<$20% fat (39). Therefore, participants with NAFLD with 5–20% fat in their liver might have been categorized in the non-NAFLD group (40). However, routine liver biopsy is not recommended in all patients with NAFLD (16–18); thus, US is recommended as the first-line imaging technique for diagnosing NAFLD (16). Therefore, the current study's use of US to diagnose NAFLD is easily applicable to clinical practice. Third, intraobserver, interobserver, or interequipment differences in US examinations were not assessed. However, US was performed by experienced technicians, and physicians rechecked the US image with an instant film. Intraobserver, interobserver, and interequipment differences were less likely to affect the association between NAFLD and T2DM incidence because the

technicians and physicians were blinded to the aim of the study. Fourth, information about alcohol intake was self-reported and, therefore, might have inaccuracies. Considering this possibility, subgroup analyses in never-drinkers and participants with GGT <100 units/L were conducted. The results were consistent with the overall results. Finally, this was a retrospective study involving a single ethnic group, and there was a lack of oral glucose tolerance test, waist circumference, and HOMA-IR data.

In conclusion, the present 10-year cohort study showed that NAFLD is an independent risk factor for T2DM incidence regardless of sex. Hence, clinicians should be aware of the long-term effects of NAFLD on T2DM. Of note, NAFLD improvement is associated with significant T2DM incidence reduction. This causal relationship warrants clarification in future studies.

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