ORIGINAL ARTICLE

Journal of Diabetes   WILEY

Nonalcoholic fatty liver disease in relation to the remission and progression along the glycemic continuum

Zhuojun Xin[1,2] | Jiaojiao Huang[1,2] | Qiuyu Cao[1,2] | Jialu Wang[1,2] |
Ruixin He[1,2] | Tianzhichao Hou[1,2] | Yi Ding[1,2] | Jieli Lu[1,2] | Min Xu[1,2] |
Tiange Wang[1,2] | Zhiyun Zhao[1,2] | Weiqing Wang[1,2] | Guang Ning[1,2] |
Yufang Bi[1,2] | Yu Xu[1,2] | Mian Li[1,2]

[1]Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[2]Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the PR China, Shanghai Key Laboratory for Endocrine Tumor, State Key Laboratory of Medical Genomics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence
Mian Li, MD, PhD, Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the People's Republic of China, Shanghai National Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin 2nd Road, Shanghai 200025, China.
Email: limian39@aliyun.com

Yu Xu, MD, PhD, Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the People's Republic of China, Shanghai National Center for Translational Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin 2nd Road, Shanghai 200025, China.
Email: jane.yuxu@gmail.com

Abstract

Background: The study aimed to explore the associations of nonalcoholic fatty liver disease (NAFLD) with the remission and progression along the glycemic continuum.

Methods: This prospective cohort study was performed among the general population in 2010–2015. NAFLD was defined as ultrasound-detected hepatic steatosis with absence of excessive alcohol consumption and other hepatic diseases. Remission of type 2 diabetes referred to glycated hemoglobin <6.5% without hypoglycemic agents for ≥3 months. Prediabetes remission referred to normalization of blood glucose. Multivariable logistic analysis was applied to identify the risk of glycemic metabolic transition.

Results: During a median follow-up of 4.3 years, participants with NAFLD had a significantly higher risk of progressing from normal glucose tolerance to diabetes (3.36 [1.60–7.07]) and lower likelihood of diabetes remission (0.48 [0.30–0.78]). Associations in participants with overweight or obesity and higher probability of hepatic fibrosis remained consistent. Results related to the effect of NAFLD on the specific glucose parameters were generally in line with the changes of glycemic status. NAFLD improvement decreased the risk of prediabetes progressing to diabetes (0.50 [0.32–0.80]) and increased the probability of prediabetes remission (2.67 [1.49–4.79]). NAFLD tended to show the most significant association with glycemic progression and decreased the likelihood in remission of prediabetes and diabetes.

Conclusions: Presence of NAFLD increased risk of glycemic progression and decreased likelihood of remission. NAFLD improvement mitigated glycemic deterioration, whereas NAFLD progression impeded the chance of remission. The results emphasized joint management of NAFLD and diabetes and further focused on liver-specific subgroups of diabetes to tailor early intervention.

KEYWORDS
epidemiology, glycemic profile, nonalcoholic fatty liver disease, remission, type 2 diabetes

Highlights
- To what extent NAFLD is associated with glycemic remission among the general population remains unclear.
- The study elaborated that presence of NAFLD and fibrosis status decreased the chance of glycemic remission whereas NAFLD improvement mitigated glycemic deterioration, emphasizing joint management to liver-focused subgroups of diabetes.

1 | INTRODUCTION

Type 2 diabetes (T2D), now has reached epidemic proportions, affecting 10.5% adults worldwide and 10.6% in China, imposing great burden not only on individuals but also society.[1] T2D has been perceived as progressive and irreversible condition for a long time.[2,3] Recently, accumulating evidence based on intensive lifestyle intervention studies has proved the attainability of T2D remission, such as the Diabetes Remission Clinical Trial (DiRECT) study, which achieved 46% remission among short-duration T2D, apart from bariatric surgery and intensive insulin therapy.[4–6] Nevertheless, participants have inconsistent response to intensive lifestyle intervention, indicating that there were individual differences in the achievement of T2D remission. Results from the DiRECT study demonstrated that remission of T2D caused by sufficient weight loss was largely depended on the decrease in hepatic fat content, implying the critical role of hepatic fat accumulation in T2D remission.[7]

In 2021, the American Diabetes Association (ADA) proposed the definition and interpretation of remission in T2D, as well as an urgent need to detect potential predictors for remission.[8] Nevertheless, outside of the context of clinical trials, data are still limited regarding the characteristics of people who were in remission of T2D in normal care. Recently, a retrospective cohort study has detected the inverse association of fatty liver and T2D remission among 2567 diabetic Japanese over a 2-year follow-up period, for the first time indicating a potential effect of nonalcoholic fatty liver disease (NAFLD) on T2D remission in a real world situation.[9] Actually, on account of the prevalence and long-term risk related to

prediabetes, prediabetes and T2D were recognized as a continuum of glucose intolerance, which raised the importance to recognize the potential markers of progression and remission on the unidirectional road of glycemic metabolism.

Hence, based on a prospective cohort study among the Chinese general population, the current study aimed to further fill the following gaps: (1) associations of NAFLD status with the remission and progression across normal glucose tolerance (NGT), prediabetes, and T2D and the change of the glycemic metrics along the glycemic continuum; and (2) associations of changes of NAFLD status and degrees of fibrosis status with glycemic metabolic transition.

2 | METHODS

2.1 | Study design and population

The study was launched among a community-based population in Jiading District of Shanghai, China between March and August 2010. The protocol has been described in detail elsewhere.[10] Briefly, a total of 10 375 registered residents aged ≥40 years were recruited and completed a baseline health examination, including a comprehensive standard questionnaire and clinical measurements. After a follow-up of up to 5 years, the enrolled participants were reinvited for a follow-up visit during August 2014 and May 2015. For the current analysis, participants with indeterminate information on identification of NAFLD and glycemic status were excluded: (1) missing data on baseline glucose parameters ($n = 34$); (2) incompletion of

hepatic ultrasound ($n = 42$); (3) excessive alcohol consumption ($n = 971$) and liver diseases other than fatty liver ($n = 333$); (4) registered for death during the follow-up ($n = 224$); (5) inaccessible to onsite follow-up visit ($n = 3058$); and (6) indeterminate to identify glycemic status at follow-up ($n = 42$). To detect the NAFLD status changes between two visits, missing data on the definition of follow-up NAFLD were further excluded ($n = 590$). Finally, 5671 participants were included in the analysis of associations of NAFLD with progression and remission of glycemic metabolism, and 5081 were analyzed for NAFLD status changes, respectively. Detailed selection procedure was presented in Figure 1. The study protocol was endorsed by the Institutional Review Board of Rui-Jin Hospital. Detailed written informed consent was obtained from each participant.

2.2 | Measurements

Data on demographic profile, educational attainment, lifestyle factors (including cigarette smoking, alcoholic consumption, and physical activity) and medical history were collected at baseline and follow-up visits by standard questionnaires face to face. Self-reported illness and medication will be further confirmed by the carry-on medical records. Physical activity was assessed by the short form of the Global Physical Activity Questionnaire and was classified into two groups: ≥600 metabolic equivalent minutes per week (MET-min/week) or not[11] Body weight, height, and blood pressure were measured by trained staff on the basis of a standard protocol.[12] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

All participants underwent an oral glucose tolerance test after an overnight fasting (>10 h). Fasting and 2-hour postprandial plasma glucose were measured by the glucose oxidase method on an automated analyzer (Modular Analytics P800; Roche). Glycated hemoglobin (HbA1c) was determined by high-performance liquid chromatography using the VARIANT II Hemoglobin Testing System (Bio-Rad Laboratories). Fasting serum insulin and biochemical parameters, including total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol, as well as liver enzymes (including alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl-transferase) were measured on auto-analyzers (Modular E170; Roche).

2.3 | Ultrasound-based definition of NAFLD

Liver ultrasound was performed separately by two clinical sonographers, using a high-resolution B-mode tomographic ultrasonic system (Esaote Biomedica SpA, Italy) with a 3.5-MHz probe. Fatty liver was detected by the presence of ≥2 of following three imaging findings: (1) diffusely increased echogenicity of the liver relative to
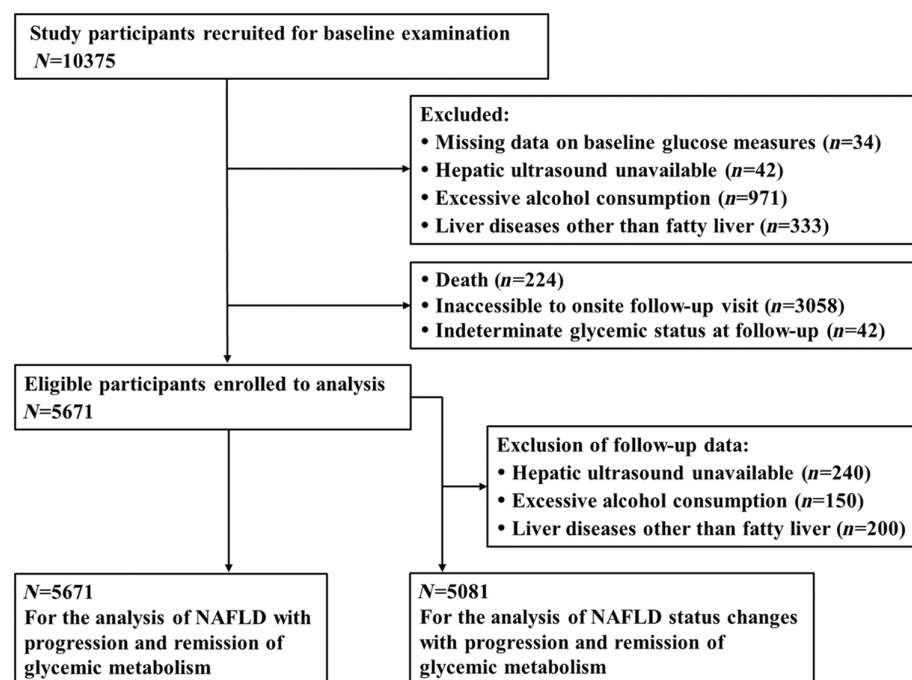

FIGURE 1   Study population flow diagram. NAFLD, non-alcoholic fatty liver disease.

the kidney, (2) ultrasound beam attenuation, or (3) poor visualization of intrahepatic structures. A third sonographer, who was blinded to the study, was required if there was contradictory between the former two diagnosis of fatty liver. Definition of NAFLD was based on ultrasound-detected fatty liver with absence of excessive alcohol consumption and other hepatic diseases.[13,14]

To further clarify associations of NAFLD status changes and glycemic metabolism, the presence of NAFLD was evaluated both at baseline and follow-up visits. Study participants were classified into four groups according to the two visits' presence status of NAFLD: (1) stable non-NAFLD; (2) new-onset NAFLD; (3) stable NAFLD; and (4) NAFLD improvement, respectively.

The probability of hepatic fibrosis was assessed by the invasive index of fibrosis-4 (FIB-4) and was calculated as follows: FIB-4 = age (years) × aspartate aminotransferase (U/L)/(platelet count $[\times 10^9/L] \times$ alanine aminotransferase $[U/L]^{1/2}$). Higher probability of hepatic fibrosis was identified as FIB-4 ≥ 1.3.[15]

2.4 | Definition of glycemic status

T2D was diagnosis as HbA1c ≥ 6.5% or fasting plasma glucose ≥126 mg/dl or 2-h postprandial plasma glucose ≥200 mg/dl, or with a previous diagnosis of diabetes, according to the ADA criteria.[16] Prediabetes was defined as HbA1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dl, or 2-h postprandial plasma glucose 140–199 mg/dl. The index of homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting serum insulin (μIU/ml) × fasting plasma glucose (mmol/L)/22.5. HOMA-IR ≥ 2.5 was defined as insulin resistance.[17]

Glycemic progression referred to (1) NGT at baseline progressing to new-onset diabetes and new-onset prediabetes at follow-up, and (2) baseline prediabetes status progressing to diabetes at follow-up, respectively.

Glycemic remission contained remission of type 2 diabetes and prediabetes at follow-up. According to ADA consensus updated in 2021, remission of T2D referred to HbA1c below 6.5% on the premise of not prescribing conventional hypoglycemic agents for at least 3 months.[8] Prediabetes remission referred to normalization of blood glucose (HbA1c < 5.7% and fasting plasma glucose <100 mg/dl and 2-hour postprandial plasma glucose <140 mg/dl). The routine medication history of insulin or hypoglycemic agents was first obtained by the standard question "Have you ever injected insulin or taken any hypoglycemic agents in the past 3 months?" and then confirmed according to the medical records.

2.5 | Statistical analysis

Continuous variables were presented by means ± SD or medians (interquartile ranges), and categorical variables were expressed in numbers (percentages). Baseline characteristics were summarized according to the combination of the baseline status of NAFLD and glycemic metabolism.

Multivariable logistic model was fitted to investigate associations of NAFLD status with progression and remission of glycemic metabolism. Study population was divided into three groups according to baseline glycemic status: NGT, prediabetes, and diabetes. To specify the progression and remission of glycemic metabolism, stable glycemic status evaluated at baseline and follow-up visits, including stable NGT, stable prediabetes, and stable diabetes were regarded as reference outcomes in respective groups. Odds ratio (OR) and 95% confidence interval (CI) were calculated after potential adjustments for age, sex, follow-up interval (model 1), current smoking and drinking status (yes or no), education levels (<9 years or ≥9 years), physical activity (<600 MET-min/week or ≥ 600 MET-min/week), BMI, family history of diabetes (yes or no), hypertension (yes or no) (model 2), LDL-cholesterol, HDL-cholesterol, and triglycerides (model 3). Changes of specific glucose parameters (HbA1c, fasting glucose, 2-h glucose, and status of insulin resistance) were also analyzed. Categories of normal, impaired/elevated, and diabetic status were corresponding to the diagnostic ranges of NGT, prediabetes, and diabetes, respectively. For the analysis of NAFLD status changes and glycemic metabolism, the presence of NAFLD was evaluated not only at baseline but also follow-up visit. Associations between NAFLD changes and transition of glycemic metabolism were further explored.

Statistical analysis was performed on SAS 9.2 and a two-tailed p value <.05 was of statistical significance.

3 | RESULTS

3.1 | General characteristics

Baseline characteristics of the included 5671 participants in the associations of NAFLD with progression and remission of glycemic metabolism were summarized in Table 1 according to the combination of the baseline status of NAFLD and glycemic metabolism. In the analyzed population, 1747 (30.8%) were NAFLD and 3924 (69.2%) were non-NAFLD. Mean ages in the two groups were 58.2 (8.3) and 58.0 (9.0), respectively. In general, NAFLD participants had a worse performance in the baseline metabolic characteristics compared with non-NAFLD counterparts (all $p < .05$). Combined with the baseline glycemic

TABLE 1 Baseline characteristics of study population according to the presence of NAFLD and glycemic status at baseline

	NAFLD	Non-NAFLD	NGT	Prediabetes	Diabetes	p for trend	NGT	Prediabetes	Diabetes	p for trend
No. of participants, n (%)	1747 (30.8)	3924 (69.2)	330 (18.9)	781 (44.7)	636 (36.4)	-	1713 (43.7)	1720 (43.8)	491 (12.5)	-
Age, year	58.2 ± 8.3	58.0 ± 9.0	55.3 ± 7.7	58.1 ± 8.1	59.8 ± 8.4	<.0001	55.7 ± 8.7	59.2 ± 8.8	61.9 ± 8.7	<.0001
Male, n (%)	533 (30.5)	1143 (29.13)	112 (33.9)	210 (26.9)	211 (33.2)	.6850	488 (28.5)	467 (27.2)	188 (38.3)	.0039
High school or above, n (%)	346 (19.8)	776 (19.8)	85 (25.8)	145 (18.6)	116 (18.2)	.0139	388 (22.7)	288 (16.7)	100 (20.4)	.0064
Current smoking, n (%)	309 (17.7)	655 (16.7)	70 (21.2)	118 (15.1)	121 (19.0)	.7864	311 (18.2)	260 (15.1)	84 (17.1)	.1482
Current drinking, n (%)	223 (12.8)	462 (11.8)	52 (15.8)	90 (11.5)	81 (12.7)	.3182	208 (12.1)	184 (10.7)	70 (14.3)	.6695
Family history of diabetes, n (%)	268 (15.4)	383 (9.8)*	36 (10.9)	93 (11.9)	139 (21.9)	<.0001	128 (7.5)	140 (8.2)	115 (23.5)	<.0001
Physical activity ≥ 600 MET-min/week, n (%)	1233 (70.6)	2828 (72.1)	241 (73.0)	537 (68.8)	455 (71.5)	.8862	1225 (71.5)	1241 (72.2)	362 (73.7)	.3559
Body mass index (kg/m^2)	27.5 ± 3.0	24.2 ± 2.8*	27.3 ± 2.8	27.5 ± 2.9	27.7 ± 3.3	.0715	23.9 ± 2.7	24.3 ± 2.8	24.6 ± 3.1	<.0001
Waist circumference (cm)	88.6 ± 7.8	79.4 ± 7.7*	88.1 ± 7.1	88.0 ± 7.6	89.8 ± 8.3	.0002	78.4 ± 7.6	79.7 ± 7.6	81.9 ± 7.7	<.0001
Systolic BP (mmHg)	146.6 ± 19.1	139.0 ± 19.9*	140.5 ± 17.1	146.4 ± 18.8	150.0 ± 19.7	<.0001	134.9 ± 19.6	140.8 ± 19.4	147.5 ± 19.2	<.0001
Diastolic BP (mmHg)	85.6 ± 10.3	81.4 ± 10.0*	85.0 ± 9.7	86.0 ± 10.3	85.4 ± 10.6	.8525	80.8 ± 10.1	82.0 ± 9.8	81.5 ± 10.3	.0138
Fasting glucose (mg/dl)	109.8 ± 35.6	95.8 ± 21.2*	88.3 ± 7.2	96.7 ± 10.7	136.9 ± 46.0	<.0001	86.9 ± 6.9	94.8 ± 10.3	129.9 ± 40.1	<.0001
Postprandial glucose (mg/dL)	185.5 ± 92.8	134.2 ± 65.0*	111.2 ± 20.0	142.4 ± 30.3	277.2 ± 93.8	<.0001	103.3 ± 20.1	128.9 ± 31.5	261.9 ± 96.6	<.0001
HbA1c (%)	6.2 ± 1.2	5.7 ± 0.7*	5.4 ± 0.2	5.8 ± 0.3	7.1 ± 1.5	<.0001	5.3 ± 0.2	5.7 ± 0.3	6.8 ± 1.5	<.0001
HOMA-IR	2.6 (1.8-3.8)	1.4 (1.0-1.9)*	2.0 (1.5-2.7)	2.4 (1.8-3.3)	3.5 (2.4-5.2)	<.0001	1.2 (0.9-1.7)	1.4 (1.0-2.0)	2.0 (1.3-3.1)	<.0001
Total cholesterol (mg/dl)	213.0 ± 42.7	205.4 ± 37.7*	204.4 ± 36.9	215.9 ± 46.1	214.1 ± 40.6	.0060	200.6 ± 37.3	209.2 ± 36.9	208.9 ± 40.2	<.0001
Triglycerides (mg/dl)	164.6 (120.4-229.2)	109.7 (80.5-149.6)*	158.0 (113.3-212.4)	164.6 (120.4-228.3)	169.5 (122.6-231.4)	.0113	102.7 (77.0-140.7)	111.5 (82.3-155.8)	122.1 (89.4-158.4)	<.0001
LDL-cholesterol (mg/dl)	128.0 ± 35.1	123.1 ± 32.6*	121.7 ± 31.9	130.2 ± 36.2	128.6 ± 35.0	.0209	119.0 ± 32.3	126.0 ± 31.6	127.6 ± 35.3	<.0001
HDL-cholesterol (mg/dl)	46.7 ± 10.4	53.2 ± 12.4*	45.6 ± 10.5	47.1 ± 10.2	46.8 ± 10.6	.1870	53.5 ± 12.1	53.5 ± 12.8	51.1 ± 12.0	.0028
Alanine aminotransferase (IU)	23.2 (17.4-33.4)	16.5 (12.9-21.8)*	20.3 (15.8-27.6)	22.9 (17.4-32.1)	25.0 (18.1-38.8)	<.0001	16.0 (12.6-21.1)	16.7 (13.2-21.6)	17.6 (13.4-23.8)	<.0001
Aspartate aminotransferase (IU)	22.4 (19.0-27.4)	21.1 (18.1-24.6)*	21.1 (17.9-25.3)	22.6 (19.2-27.4)	23.0 (19.4-29.8)	<.0001	20.9 (18.0-24.4)	21.5 (18.5-24.9)	20.2 (16.9-24.6)	.8902
γ-glutamyl transferase (IU)	29.0 (10.0-44.0)	18.0 (13.0-26.0)*	23.0 (17.0-36.0)	28.0 (20.0-43.0)	32.0 (22.0-50.0)	<.0001	16.0 (12.0-24.0)	18.0 (14.0-26.0)	21.0 (16.0-31.0)	<.0001
Fibrosis-4 ≥ 1.3, n (%)	791 (45.3)	2246 (57.2)*	143 (43.3)	345 (44.2)	303 (47.6)	.1537	940 (54.9)	1026 (59.7)	280 (57.0)	.0619

*p < .05 for baseline differences between the NAFLD and non-NAFLD groups. Abbreviations: BP, blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; MET-min/week, metabolic equivalent minutes per week; NAFLD, non-alcoholic fatty liver disease; NGT, normal glucose tolerance.

**TABLE 2** Presence of NAFLD with progression and remission of glycemic metabolism

	No. of cases/ participants NAFLD (+) versus NAFLD (−)	Baseline NAFLD (−)	Baseline NAFLD (+)					
			Model 1 (OR [95% CI])	p value	Model 2 (OR [95% CI])	p value	Model 3 (OR [95% CI])	p value
Among participants with NGT (n = 2043)								
NGT to prediabetes (n = 995)	188/330 versus 807/1713	1.00 (ref.)	1.64 (1.28–2.1)	<.0001	1.31 (0.99–1.72)	.0567	1.18 (0.89–1.56)	.2531
NGT to diabetes (n = 60)	17/330 versus 43/1713	1.00 (ref.)	3.17 (1.72–5.85)	.0002	3.85 (1.87–7.96)	.0003	3.36 (1.60–7.07)	.0014
Among participants with prediabetes (n = 2501)								
Prediabetes to diabetes (n = 479)	215/781 versus 264/1720	1.00 (ref.)	1.97 (1.59–2.43)	<.0001	1.68 (1.32–2.13)	<.0001	1.69 (1.32–2.17)	<.0001
Remission of prediabetes[a] (n = 351)	68/781 versus 283/1720	1.00 (ref.)	0.55 (0.42–0.74)	<.0001	0.62 (0.45–0.85)	.0030	0.70 (0.51–0.98)	.0371
Among participants with diabetes (n = 1127)								
Remission of diabetes[b] (n = 102)	41/636 versus 61/491	1.00 (ref.)	0.48 (0.31–0.72)	.0005	0.49 (0.31–0.79)	.0033	0.48 (0.30–0.78)	.0033

Note: The stable glycemic status assessed at both baseline and follow-up visits was regarded as the reference outcome, including stable NGT to NGT, stable prediabetes, and stable diabetes. Model 1 was adjusted for age, sex, and follow-up interval; Model 2 was further adjusted for current smoking and drinking (yes or no), education levels (<9 years or ≥9 years), physical activity (<600 MET-min/week or ≥600 MET-min/week), body mass index, family history of diabetes (yes or no), hypertension (yes or no); Model 3 was further adjusted for LDL-cholesterol, HDL-cholesterol and triglycerides at baseline.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET-min/week, metabolic equivalent minutes per week; NAFLD, non-alcoholic fatty liver disease; NGT, normal glucose tolerance; OR, odds ratio.

[a]For participants with prediabetes, remission was defined as normalization of blood glucose (HbA1c < 5.7% and fasting glucose <5.6 mmol/L and postprandial glucose <7.8 mmol/L);

[b]Remission of diabetes was represented as an HbA1c <6.5% without prescribing conventional hypoglycemic agents for at least 3 months.
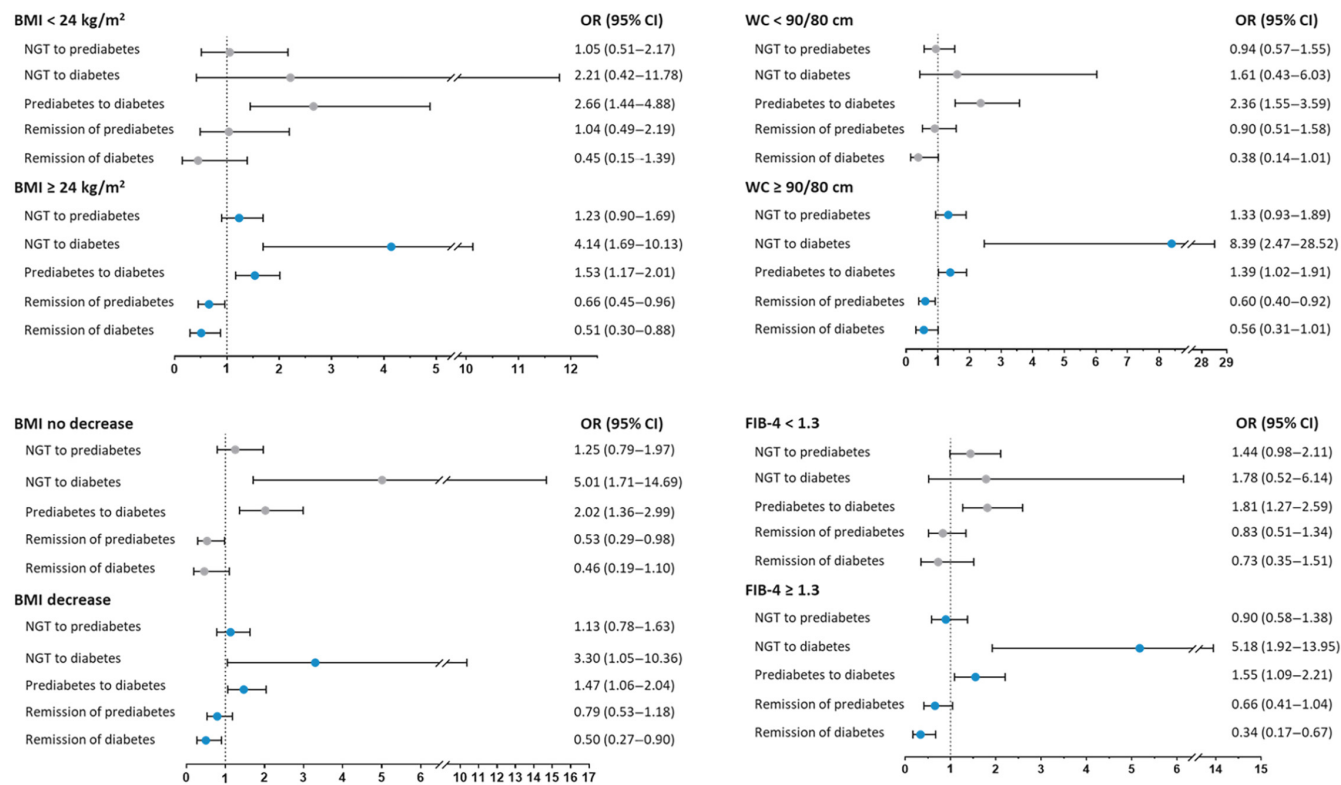
FIGURE 2 Stratified analyses according to BMI, BMI change, WC, and FIB-4. The stable glycemic status at two visits of baseline and follow-up, including stable NGT, stable prediabetes and stable diabetes were regarded as the reference outcome. Multivariable models were adjusted for age, sex, follow-up interval, current smoking and drinking (yes or no), education levels (<9 years or ≥9 years), physical activity (<600 MET-min/week or ≥ 600 MET-min/week), BMI, family history of diabetes (yes or no), hypertension (yes or no), LDL-cholesterol, HDL-cholesterol, and triglycerides at baseline. BMI, body mass index; CI, confidence interval; FIB-4, fibrosis-4; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET-min/week, metabolic equivalent minutes per week; NGT, normal glucose tolerance; OR, odds ratio; WC, waist circumference.

status, the prevalence of prediabetes and diabetes was 44.7% and 36.4% for NAFLD group and 43.8% and 12.5% for non-NAFLD group, respectively. Compared with participants in both NGT subgroups, those with prediabetes or diabetes tended to be older, with lower educational levels and higher proportion of diabetes family history (all p for trend <.05). Concerning to cardiometabolic health indicators, participants with prediabetes and diabetes had higher levels of systolic blood pressure, adipose measurements (BMI and waist circumference), glucose parameters (including fasting and 2-hour postprandial glucose, HbA1c, and HOMA-IR), lipid profiles (total cholesterol, triglycerides, and LDL-cholesterol), and liver enzymes, along with the deterioration of glucose status (all p for trend <.05).

3.2 | Presence of NAFLD with progression and remission of glycemic metabolism

Table 2 exhibited the associations of NAFLD presence with progression and remission of glycemic metabolism. During a median follow-up of 4.3 years, 57.0% (188/330) and 5.2%

(17/330) NAFLD participants with NGT progressed to new-onset prediabetes and diabetes, respectively. Meanwhile, 8.7% (68/781) and 6.4% (41/636) participants with NAFLD were in remission of prediabetes and diabetes, respectively.

Overall, the presence of NAFLD at baseline increased the risk of glycemic progression and decreased the probability of glycemic remission compared with non-NAFLD counterparts. Specifically, after adjusting for all potential confounders, participants with NAFLD had a significantly higher risk of progressing from NGT to diabetes (OR 3.36; 95% CI 1.60–7.07) and a lower likelihood of diabetes remission (OR 0.48; 95% CI 0.30–0.78) compared with the non-NAFLD group. Similar pattern of glycemic transition was additionally observed in participants with prediabetes (OR 1.69; 95% CI 1.32–2.17 for progressing from prediabetes to diabetes, and OR 0.70; 95% CI 0.51–0.98 for prediabetes remission). In the sensitivity analysis, fat-free mass (FFM) assessed by bioelectrical impedance was further adjusted based on Model 3. Results related to the risk of progressing from NGT to diabetes (OR 3.24; 95% CI 1.43–7.32), from prediabetes to diabetes (OR 1.71; 95% CI 1.31–2.23) and remission of diabetes (OR 0.45; 95% CI 0.27–0.76), remained significant (Table S1).

TABLE 3 Association of NAFLD with changes of specific glucose parameters

	No. of cases/participants NAFLD (+) versus NAFLD (−)	Baseline NAFLD (+)					
		Model 1 (OR [95% CI])	p value	Model 2 (OR [95% CI])	p value	Model 3 (OR [95% CI])	p value
HbA1c							
Stable normal (n = 2269)	415/1197 versus 1854/3332	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Normal to elevated (n = 293)	87/1197 versus 206/3332	1.80 (1.37–2.37)	<.0001	1.47 (1.07–2.02)	.0181	1.24 (0.89–1.73)	.2111
Normal to diabetic (n = 13)	7/1197 versus 6/3332	4.98 (1.65–15.00)	.0044	2.82 (0.74–10.82)	.1301	3.46 (0.72–16.62)	.1207
Stable elevated (n = 732)	213/1197 versus 519/3332	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Elevated to diabetic (n = 72)	50/1197 versus 22/3332	5.66 (3.33–9.62)	<.0001	5.38 (2.92–9.91)	<.0001	4.79 (2.48–9.28)	<.0001
Elevated to normal (n = 711)	164/1197 versus 547/3332	0.73 (0.58–0.93)	.0107	0.94 (0.72–1.23)	.6559	1.01 (0.76–1.34)	.9479
Stable diabetic (n = 413)	253/1197 versus 160/3332	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Diabetic to elevated/normal (n = 26)	8/1197 versus 18/3332	0.28 (0.12–0.67)	.0044	0.28 (0.10–0.74)	.0110	0.25 (0.08–0.77)	.0163
Fasting glucose							
Stable normal (n = 2062)	383/1204 versus 1679/3399	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Normal to impaired (n = 1398)	325/1204 versus 1073/3399	1.34 (1.14–1.59)	.0006	1.25 (1.03–1.51)	.0208	1.06 (0.87–1.30)	.5380
Normal to diabetic (n = 64)	28/1204 versus 36/3399	3.58 (2.15–5.97)	<.0001	2.68 (1.47–4.87)	.0013	2.01 (1.07–3.78)	.0291
Stable impaired (n = 459)	151/1204 versus 308/3399	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Impaired to diabetic (n = 111)	53/1204 versus 58/3399	1.88 (1.23–2.88)	.0037	1.66 (1.02–2.70)	.0426	1.49 (0.88–2.52)	.1395
Impaired to normal (n = 86)	20/1204 versus 66//3399	0.64 (0.37–1.10)	.1059	0.78 (0.42–1.44)	.4148	0.82 (0.43–1.55)	.5425
Stable diabetic (n = 410)	241/1204 versus 169/3399	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Diabetic to impaired/normal (n = 13)	3/1204 versus 10/3399	0.21 (0.06–0.79)	.0203	0.17 (0.04–0.78)	.0225	0.11 (0.02–0.84)	.0334
2-h glucose							
Stable normal (n = 2274)	345/1553 versus 1929/3672	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Normal to impaired (n = 935)	248/1553 versus 687/3672	2.10 (1.74–2.53)	<.0001	1.68 (1.36–2.07)	<.0001	1.51 (1.21–1.87)	.0002
Normal to diabetic (n = 137)	53/1553 versus 84/3672	3.75 (2.59–5.42)	<.0001	2.67 (1.75–4.08)	<.0001	2.11 (1.34–3.33)	.0012
Stable impaired (n = 495)	193/1553 versus 302/3672	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Impaired to diabetic (n = 278)	140/1553 versus 138/3672	1.62 (1.20–2.18)	.0017	1.51 (1.07–2.13)	.0180	1.65 (1.14–2.38)	.0074
Impaired to normal (n = 301)	93/1553 versus 208/3672	0.68 (0.50–0.92)	.0127	0.76 (0.53–1.07)	.1186	0.81 (0.56–1.17)	.2560
Stable diabetic (n = 736)	449/1553 versus 287/3672	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Diabetic to impaired/normal (n = 69)	32/1553 versus 37/3672	0.52 (0.32–0.86)	.0115	0.51 (0.29–0.90)	.0205	0.49 (0.26–0.95)	.0336

(Continues)

TABLE 3 (Continued)

	No. of cases/participants NAFLD (+) versus NAFLD (−)	Baseline NAFLD (+)					
		Model 1 (OR [95% CI])	p value	Model 2 (OR [95% CI])	p value	Model 3 (OR [95% CI])	p value
Insulin resistance							
Stable normal (n = 3434)	500/1741 versus 2934/3913	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Normal to resistance (n = 813)	317/1741 versus 496/3913	3.90 (3.29–4.64)	<.0001	2.68 (2.22–3.23)	<.0001	2.27 (1.87–2.75)	<.0001
Stable resistance (n = 1039)	741/1741 versus 298/3913	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Resistance to normal (n = 368)	183/1741 versus 185/3913	0.39 (0.30–0.49)	<.0001	0.51 (0.39–0.67)	<.0001	0.59 (0.44–0.78)	.0002

Note: Cutoffs of specific glucose parameters: HbA1c (normal: <5.7%; elevated: 5.7%–6.4%; diabetic: ≥6.5% among diabetes), fasting glucose (normal: <5.6; impaired: 5.6–6.9; diabetic: ≥7.0 mmol/L among diabetes), 2-h glucose (normal: <7.8 mmol/L; impaired: 7.8–11.0 mmol/L; diabetic: ≥11.1 mmol/L among diabetes), insulin resistance (normal: <2.5; resistance: ≥2.5). The stable levels of glucose parameters tested at both baseline and follow-up visits, including stable normal, stable impaired/elevated, stable diabetic, and stable resistance were regarded as the reference outcome. Model 1 was adjusted for age, sex, and follow-up interval; Model 2 was further adjusted for current smoking and drinking (yes or no), education levels (<9 years or ≥9 years), physical activity (<600 MET-min/week or ≥600 MET-min/week), body mass index, family history of diabetes (yes or no), hypertension (yes or no); Model 3 was further adjusted for LDL-cholesterol, HDL-cholesterol, triglycerides, and HbA1c at baseline in the analysis for fasting, 2-h glucose, and insulin resistance and further adjusted for fasting glucose in the analysis for HbA1c.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET-min/week, metabolic equivalent minutes per week; NAFLD, non-alcoholic fatty liver disease; NGT, normal glucose tolerance; OR, odds ratio.

Stratified analyses were further conducted according to BMI, BMI change, waist circumference, and FIB-4. As shown in Figure 2, NAFLD participants who had overweight or obesity (OR 4.14; 95% CI 1.69–10.13), central obesity (OR 8.39; 95% CI 2.47–28.52), or higher probability of hepatic fibrosis (OR 5.18; 95% CI 1.92–13.95) were associated with an elevated risk of progressing from NGT to diabetes and lower likelihood of diabetes remission (OR 0.51; 95% CI 0.30–0.88 among those with overweight or obesity; OR 0.34; 95% CI 0.17–0.67 among those with higher probability of hepatic fibrosis, respectively). Similar trend of glycemic transition was observed in participants with prediabetes. The level of BMI from baseline to the follow-up visit tended to decrease (26.3 ± 3.5 vs. 25.8 ± 3.8 kg/m^2) and the population was stratified into BMI decrease or not. The analysis showed that presence of NAFLD increased the risk of incident diabetes (OR 5.01; 95% CI 1.71–14.69) and impeded prediabetes remission (OR 0.50; 95% CI 0.27–0.90) even in participants without BMI decrease.

3.3 | Association of NAFLD with changes of specific glucose parameters

In addition to elaborating the overall transition of glycemic status, we further investigated the association of NAFLD with changes of specific glucose parameters. Findings from Table 3 showed that NAFLD was involved in the whole process of glucose regulation, including HbA1c, fasting glucose, 2-h glucose, and status of insulin resistance. With regard to HbA1c, an indicator of overall level of recent 2–3 months' glycemic status, its increased risk of progressing from elevated level to diabetes (OR 4.79; 95% CI 2.48–9.28) and decreased likelihood of regressing from diabetes to elevated or normal level (OR 0.25; 95% CI 0.08–0.77) were observed among participants with NAFLD. Significant similarities were found in the progression and remission of fasting glucose and 2-h glucose parameters. As for the status of insulin resistance, NAFLD participants were more likely to get involved in the deterioration (OR 2.27; 95% CI 1.87–2.75) and less likely to improve to the normal status (OR 0.59; 95% CI 0.44–0.78). Results related to the effect of NAFLD on the glucose parameters were generally consistent with the changes of glycemic status presented in Table 2.

3.4 | NAFLD status changes with progression and remission of glycemic metabolism

Considering the mutual interaction between NAFLD and glycemic metabolism, NAFLD improvement to some
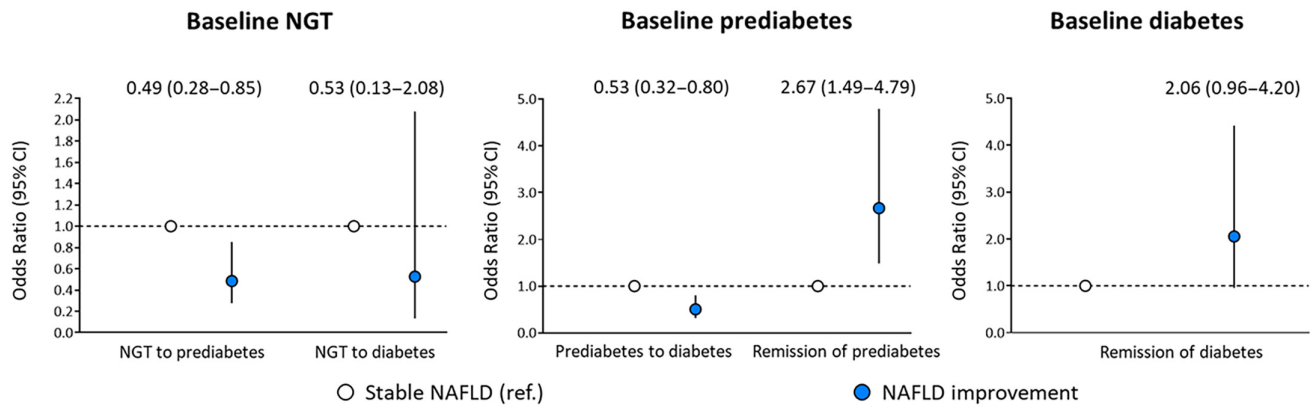
Baseline NGT

Baseline prediabetes

Baseline diabetes

No. of Cases / Participants	NGT to prediabetes	NGT to diabetes	Prediabetes to diabetes	Remission of prediabetes	Remission of diabetes
Stable NAFLD	129/206	11/206	171/549	32/549	21/413
NAFLD improvement	44/97	6/97	29/176	29/176	15/159

FIGURE 3 NAFLD improvement with changes of glycemic metabolism. The stable glycemic status at two visits of baseline and follow-up, including stable NGT, stable prediabetes, and stable diabetes were regarded as the reference outcome. Multivariable models were adjusted for age, sex, follow-up interval, current smoking and drinking (yes or no), education levels (<9 years or ≥9 years), physical activity (< 600 MET-min/week or ≥ 600 MET-min/week), BMI, family history of diabetes (yes or no), hypertension (yes or no), LDL-cholesterol, HDL-cholesterol, triglycerides, HOMA-IR at baseline, and Δ BMI. NGT, normal glucose tolerance; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; MET-min/week, metabolic equivalent minutes per week; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.
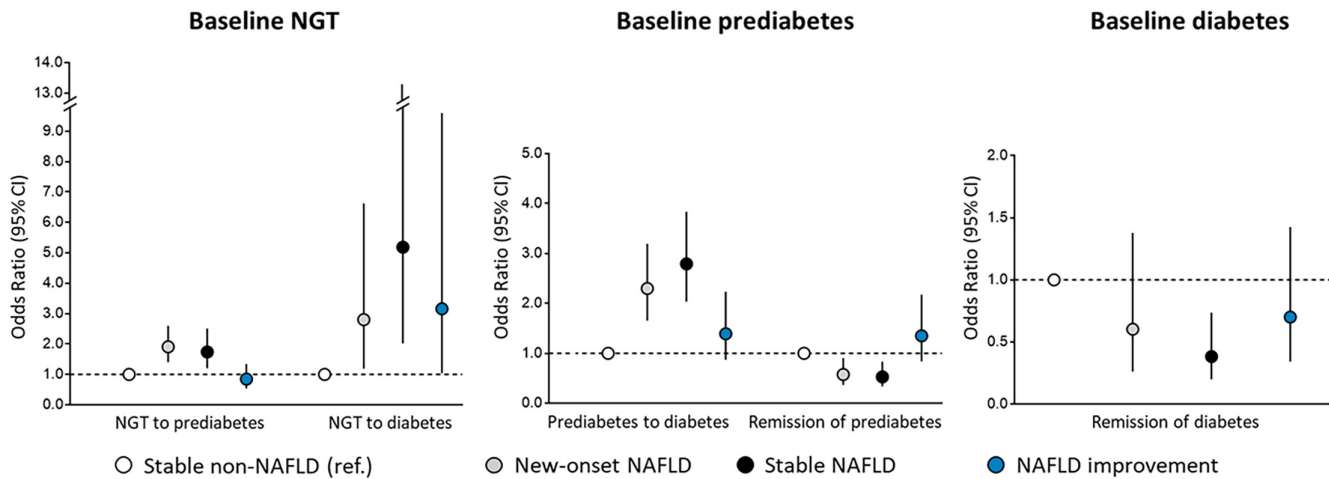
Baseline NGT

Baseline prediabetes

Baseline diabetes

No. of Cases / Participants	NGT to prediabetes	NGT to diabetes	Prediabetes to diabetes	Remission of prediabetes	Remission of diabetes
Stable non-NAFLD	572/1284	29/1284	221/1224	151/1224	43/309
New-onset NAFLD	157/252	10/252	27/313	84/313	8/99
Stable NAFLD	129/206	11/206	32/549	171/549	21/413
NAFLD improvement	44/97	6/97	29/176	29/176	15/159

FIGURE 4 NAFLD status changes with progression and remission of glycemic metabolism. The stable glycemic status at two visits of baseline and follow-up, including stable NGT, stable prediabetes, and stable diabetes were regarded as the reference outcomes. Multivariable models were adjusted for age, sex, follow-up interval, current smoking and drinking (yes or no), education levels (<9 years or ≥9 years), physical activity (<600 MET-min/week or ≥ 600 MET-min/week), BMI, family history of diabetes (yes or no), hypertension (yes or no), LDL-cholesterol, HDL-cholesterol, triglycerides, HOMA-IR at baseline, and Δ BMI. BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; MET-min/week, metabolic equivalent minutes per week; NAFLD, non-alcoholic fatty liver disease; NGT, normal glucose tolerance; OR, odds ratio.

extent mitigated the effect on the progression and remission of glycemic metabolism compared with no NAFLD improvement (Figure 3). In particular, NAFLD improvement decreased the risk of prediabetes progressing to new-onset diabetes (OR 0.50; 95% CI 0.32–0.80) and increased the probability of prediabetes remission (OR 2.67; 95% CI 1.49–4.79), respectively. Moreover, it had a marginally promoting effect on diabetes remission (OR 2.06; 95% CI 0.96–4.42).

During the follow-up period, NAFLD was in a dynamic changing condition. In addition to NAFLD improvement, associations of varying progression of NAFLD, including new-onset NAFLD and stable NAFLD status with glycemic metabolism should also be considered (Figure 4). Compared with participants who remained stable non-NAFLD status, NAFLD status changes were associated with glycemic transition at different degrees, of which stable NAFLD tended to show the most significant association with progression of glycemic metabolism, including from NGT to prediabetes (OR 1.74; 95% CI 1.21–2.51) and to diabetes (OR 5.19; 95% CI 2.02–13.29), as well as from baseline prediabetes to diabetes (OR 2.79; 95% CI 2.03–3.83). Meanwhile, stable NAFLD contributed to the least likelihood in remission of prediabetes (OR 0.53; 95% CI 0.34–0.83) and diabetes (OR 0.38; 95% CI 0.20–0.74), respectively.

4 | DISCUSSION

In this prospective study of community-based population, we illustrated that the presence of NAFLD was associated with increased risk of glycemic progression and decreased likelihood of remission. Participants with overweight or obesity and higher probability of liver fibrosis tended to aggravate this risk. The association remained consistent with changes of specific glucose parameters, which indicated that NAFLD was involved in the whole process of glucose regulation. In addition, NAFLD status changes simultaneously influenced the transition of glycemic metabolic status, of which NAFLD improvement mitigated the deterioration of glycemic transition whereas NAFLD progression further impeded the likelihood of glycemic remission. Our findings investigated a comprehensive association between NAFLD status and remission and progression along the glycemic continuum, suggesting that diabetes remission and prediabetes normalization were achievable clinical targets among NAFLD population and emphasizing that improvement of liver fat content was conductive to promote glycemic remission.

Recently, the feasibility of diabetes remission has reignited great interest. ADA proposed "remission" as the most appropriate descriptive term and updated the criteria of remission to support future clinical practice.[8] However, how common the remission of T2D was among the general population remained poorly reported. A cohort investigation from Scotland estimated 4.8% of the prevalence of T2D remission in 2019 among 162 316 national T2D register.[18] The study further summarized that participants in remission tended to be older, have a lower HbA1c at diagnosis, with no history of antidiabetic prescription, succeed in any weight loss from diagnosis, and have had previous history of bariatric surgery, comparing to participants who did not achieve remission, which were coincided with experience from previous intervention studies.[19,20] Therefore, ascertainment of those characteristics contributed to the identification of individuals with T2D who were most likely to achieve and maintain remission, which was important for making informed decisions regarding relevant T2D management and intervention.

As NAFLD and T2D have been known to coexist, share common pathogenic factors, and act in synergy to increase the risk of adverse clinical outcomes, assessment of liver fat content was equally essential for the evaluation of T2D remission.[21–23] DiRECT was the first randomized clinical trial to assess the diabetes remission as the primary outcome, which reported 46% of T2D remission at 12 months.[4] Further discussion regarding the responders who returned to the normal glucose homeostasis was observed in those with profound reduction in liver fat content. The dramatic and sustained normalization of liver fat content was associated with a fall in both plasma triglyceride concentration and intrapancreatic fat content, which contributed to the decreased exposure of β cell to fat metabolites and ultimately β cell function recovery,[7] suggesting that improving liver fat accumulation was the critical segment to achieving T2D remission.

The association of liver fat accumulation and diabetes remission in population observation study was first reported in Japanese in a 2-year cohort study.[9] Among 2567 diabetic participants, presence of fatty liver at baseline was associated with 49% decreased odds of T2D remission. Our findings were in line with the study by assessing a 52% lower probability of T2D remission for NAFLD participants and extended the knowledge to the whole glycemic continuum based on a general population. The results showed that presence of NAFLD not only brought about a decreased likelihood of T2D remission but also 30% lower odds of normalization toward prediabetes. Meanwhile, presence of NAFLD contributed to 236% and 69% higher risks of progression from NGT and prediabetes to T2D, respectively. In addition to the overall transition of glycemic metabolic status, similar tendency was detected in associations of NAFLD and transition of specific glucose parameters, suggesting that great importance should be attached to the evaluation of

NAFLD status at very early stage of abnormal glucose metabolism. The earlier NAFLD is identified and improved, the more it can prevent or even reverse the deterioration of glucose metabolism at an earlier stage.

Coinciding with associations of NAFLD status and glycemic metabolic transition, NAFLD participants with overweight or obesity as well as higher probability of fibrosis contributed to an increased risk of glycemic progression and a lower chance of remission, which indicated that the obese status and fibrosis severity tended to be identifiable traits both in the assessment of T2D remission management and NAFLD improvement. On the other hand, there were approximately 10%–20% of individuals with lean NAFLD.[24] Lean NAFLD represented a distinct phenotype, which was more correlated with metabolic changes, genetic variation, gut microbiota, and skeletal muscle atrophy.[25,26] Participants with lean NALFD also had metabolic abnormalities but the degree was more favorable than obese NAFLD. Conversely, changes in genetic variation were more prominent in lean NAFLD, such as the GG variant in the patatin-like phospholipase domain containing 3 (*PNPLA3*) was independently associated with nonalcoholic steatohepatitis and fibrosis.[27] Discrepancies in pathophysiological mechanisms perhaps accounted for the insignificance of progression from NGT to prediabetes or diabetes and remission of prediabetes or diabetes in lean NAFLD. Therefore, more attention should be focused on hepatic progression in participants with lean NAFLD. Additionally, it was noteworthy that glycemic dysregulation facilitated by NAFLD was independent of BMI change.

With the influence of lifestyle change, NAFLD is simultaneously in a dynamic changing condition. Therefore, NAFLD status changes should be taken into consideration in the transition of glycemic metabolic status. Apart from the improvement of NAFLD, progression of NAFLD was further grouped into new-onset NAFLD and stable NAFLD. We found that NAFLD improvement was associated with promotion of the remission of T2D and prediabetes, whereas new-onset NAFLD and stable NAFLD impeded the process of remission to a large extent. In addition, previous studies demonstrated that participants with diabetes and coexistence of hepatic steatosis preoperatively experienced better long-term glycemic outcomes and predicted a higher chance of T2D remission after gastric bypass surgery, which indirectly reflected the positive effect toward the improvement of hepatic fat.[28]

To the best of our acknowledge, it was the first time to comprehensively assess the associations of NAFLD status changes with progression and remission across a whole spectrum of glycemic continuum. It was highlighted that NAFLD status changes were involved in the whole process of glycemic metabolism. Combined

with the mechanism foundation of liver fat accumulation and diabetes remission strengthened by DiRECT and a previous study examining the associations of early abnormal glycemic levels with development and resolution of NAFLD in nondiabetic individuals,[29] current analysis added a certain weight to the causal relationship of the two metabolic diseases.[21] Moreover, NAFLD and T2D are often termed comorbidities, driven by the failure to efficiently sequester excess energy, not only sharing interconnected pathogenic factors but also for the synergetic development and progression of end-organ dysfunction, such as arteriosclerotic cardiovascular disease and progressive chronic kidney disease.[30] Therefore, our findings stressed the necessity of joint prevention and control on both liver and glucose metabolism.

Several limitations still merited consideration. First, fatty liver was diagnosed by ultrasonography without clarifying the specific liver fat content. However, accumulating evidence has demonstrated that ultrasound-based screening of fatty liver was applicable in a large-scale on-site epidemiological investigation.[31] Second, data on the duration of diabetes were not accessible so we did not adjust it in models. Because the analysis of glycemic metabolism was not only pointed at diabetes but also transition of prediabetes and normoglycemia, duration of diabetes was not applicable in the latter. Third, skeletal muscle mass is a nonnegligible factor associated with both NAFLD and diabetes remission.[32,33] Precise assessment of skeletal muscle mass (such as dual energy X-ray absorption) was lacking but we used the surrogate biomarker of FFM in a sensitivity analysis to improve the robustness.[34]

5 | CONCLUSIONS

Current novel findings elaborated that presence of NAFLD increased risk of glycemic progression and decreased likelihood of prediabetes or T2D remission. NAFLD improvement mitigated the deterioration of glycemic transition, whereas NAFLD progression impeded the chance of remission to a large extent. Therefore, participants with NAFLD require ongoing support to forestall both progression of hepatic outcome and glycemic metabolism. The results emphasized joint management of NAFLD and T2D and further focused on identifying liver-specific subgroups of diabetes to tailor and target early intervention to participants who would benefit most.

DATA AVAILABILITY STATEMENT
The datasets generated and/or analyzed are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

ORCID
Jieli Lu https://orcid.org/0000-0003-1317-0896
Min Xu https://orcid.org/0000-0003-3930-8718
Tiange Wang https://orcid.org/0000-0003-0723-489X
Zhiyun Zhao https://orcid.org/0000-0001-5950-2732
_Yu Xu_ https://orcid.org/0000-0003-1045-8309
Mian Li https://orcid.org/0000-0001-6514-2729

REFERENCES
1. International Diabetes Federation https://diabetesatlas.org/data/en/country/42/cn.html
2. World Health Organization. Global Report on Diabetes 2016. [cited 2020 Jul 30]. Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf.
3. Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of remission in adults with type 2 diabetes: the diabetes & aging study. _Diabetes Care_. 2014;37(12):3188-3195. doi:10.2337/dc14-0874
4. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. _Lancet (London, England)_. 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1
5. Mingrone G, Panunzi S, De Gaetano A, et al. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-Centre, randomised controlled trial. _Lancet (London, England)_. 2021; 397(10271):293-304. doi:10.1016/S0140-6736(20)32649-0
6. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. _The Lancet Diabetes & Endocrinology_. 2013; 1(1):28-34. doi:10.1016/S2213-8587(13)70006-8
7. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. _Cell Metab_. 2018;28(4):547-556.e3. doi:10.1016/j.cmet.2018.07.003
8. Riddle MC, Cefalu WT, Evans PH, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. _Diabetes Care_. 2021;44(10):2438–2444. doi:10.2337/dci21-0034
9. Yamazaki H, Wang J, Tauchi S, et al. Inverse association between fatty liver at baseline ultrasonography and remission of type 2 diabetes over a 2-year follow-up period. _Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association_. 2021; 19(3):556-564.e5. doi:10.1016/j.cgh.2020.06.032
10. Wang L, Li M, Zhao Z, et al. Ideal cardiovascular health is inversely associated with nonalcoholic fatty liver disease: a prospective analysis. _Am J Med_. 2018;131(12):1515.e1-1515.e10. doi:10.1016/j.amjmed.2018.07.011
11. World Health Organization, (2021). Global Physical Activity Questionnaire (GPAQ) Analysis Guide. http://www.who.int/chp/steps/resources/GPAQ_Analysis_Guide.pdf.
12. Li M, Xu Y, Xu M, et al. Association between nonalcoholic fatty liver disease (NAFLD) and osteoporotic fracture in middle-aged and elderly Chinese. _J Clin Endocrinol Metab_. 2012;97(6):2033-2038. doi:10.1210/jc.2011-3010
13. Chitturi S, Farrell GC, Hashimoto E, et al. Non-alcoholic fatty liver disease in the Asia-Pacific region: definitions and overview of proposed guidelines. _J Gastroenterol Hepatol_. 2007; 22(6):778-787. doi:10.1111/j.1440-1746.2007.05001.x
14. Fan JG, Jia JD, Li YM, et al. Guidelines for the diagnosis and management of nonalcoholic fatty liver disease: update 2010: (published in Chinese on Chinese journal of hepatology 2010; 18:163-166). _J Dig Dis_. 2011;12(1):38-44. doi:10.1111/j.1751-2980.2010.00476.x
15. Angulo P, Bugianesi E, Bjornsson ES, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. _Gastroenterology_. 2013;145(4):782-9.e4. doi:10.1053/j.gastro.2013.06.057
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. _Diabetes Care, 34 Suppl_. 2011;1(Suppl 1): S62-S69. doi:10.2337/dc11-S062
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. _Diabetologia_. 1985; 28(7):412-419. doi:10.1007/BF00280883
18. Captieux M, Fleetwood K, Kennon B, et al. Epidemiology of type 2 diabetes remission in Scotland in 2019: a cross-sectional

population-based study. *PLoS Med.* 2021;18(11):e1003828. doi:10.1371/journal.pmed.1003828

19. Wang GF, Yan YX, Xu N, et al. Predictive factors of type 2 diabetes mellitus remission following bariatric surgery: a meta-analysis. *Obes Surg.* 2015;25(2):199-208. doi:10.1007/s11695-014-1391-y

20. Thom G, Messow CM, Leslie WS, et al. Predictors of type 2 diabetes remission in the diabetes remission clinical trial (DiRECT). *Diabetic Medicine: A Journal of the British Diabetic Association.* 2021;38(8):e14395. doi:10.1111/dme.14395

21. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. *Nat Rev Gastroenterol Hepatol.* 2021;18(9):599-612. doi:10.1038/s41575-021-00448-y

22. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. *Nat Rev Endocrinol.* 2018;14(2):99-114. doi:10.1038/nrendo.2017.173

23. Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism: Clinical and Experimental.* 2020;111S:154170. doi:10.1016/j.metabol.2020.154170

24. Vilarinho S, Ajmera V, Zheng M, Loomba R. Emerging role of genomic analysis in clinical evaluation of Lean individuals with NAFLD. *Hepatology.* 2021 Oct;74(4):2241-2250. doi:10.1002/hep.32047

25. Xu R, Pan J, Zhou W, Ji G, Dang Y. Recent advances in lean NAFLD. *Biomed Pharmacother.* 2022 Jun;29(153):113331. doi:10.1016/j.biopha.2022.113331

26. Lee MJ, Kim EH, Bae SJ, et al. Age-related decrease in skeletal muscle mass is an independent risk factor for incident nonalcoholic fatty liver disease: a 10-year retrospective cohort study. *Gut Liver.* 2019 Jan 15;13(1):67-76. doi:10.5009/gnl18070

27. Fracanzani AL, Petta S, Lombardi R, et al. Liver and cardiovascular damage in patients with Lean nonalcoholic fatty liver disease, and association with visceral obesity. *Clin Gastroenterol Hepatol.* 2017 Oct;15(10):1604-1611. doi:10.1016/j.cgh.2017.04.045

28. Vangoitsenhoven R, Wilson RL, Cherla DV, et al. Presence of liver steatosis is associated with greater diabetes remission after gastric bypass surgery. *Diabetes Care.* 2021;44(2):321-325. doi:10.2337/dc20-0150

29. Wang B, Li M, Zhao Z, et al. Glycemic measures and development and resolution of nonalcoholic fatty liver disease in non-diabetic individuals. *J Clin Endocrinol Metab.* 2020 May 1;105(5):dgaa112;105:1416-1426. doi:10.1210/clinem/dgaa112

30. Thomas MC. The clustering of cardiovascular, renal, Adipo-metabolic eye and liver disease with type 2 diabetes. *Metabolism.* 2022 Mar;128:154961. doi:10.1016/j.metabol.2021.154961

31. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), & European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol.* 2016;64(6):1388-1402. doi:10.1016/j.jhep.2015.11.004

32. Pan XY, Liu WY, Zhu PW, et al. Low skeletal muscle mass is associated with more severe histological features of non-alcoholic fatty liver disease in male. *Hepatol Int.* 2022. doi:10.1007/s12072-022-10384-x

33. Nguyen NTK, Vo NP, Huang SY, Wang W. Fat-free mass and skeletal muscle mass gain are associated with diabetes remission after laparoscopic sleeve gastrectomy in males but not in females. *Int J Environ Res Public Health.* 2022 Jan 16;19(2):978. doi:10.3390/ijerph19020978

34. Abe T, Loenneke JP, Thiebaud RS. Fat-free adipose tissue mass: impact on peak oxygen uptake (VO_{2peak}) in adolescents with and without obesity. *Sports Med.* 2019 Jan;49(1):9-15. doi:10.1007/s40279-018-1020-3

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.