Diabetology & Metabolic Syndrome

RESEARCH

Open Access

Risk of incident type 2 diabetes in male NAFLD and NAFLD-free smokers: a 7-year post-cessation study

Jiarong Xie[1,2,3], Pengyao Lin[1], Linxiao Hou[2,3], Min Miao[4], Zhongwei Zhu[4], Youming Li[2,3], Chaohui Yu[2,3], Chengfu Xu[2,3*] and Lei Xu[1,2,3*]

Abstract

Background We aimed to investigate the post-cessation T2DM risk in male NAFLD and NAFLD-free smokers in a 7-year cohort study.

Methods The study population was male adults who underwent annual health checkups in a 7-year cohort study. Recent quitters were categorized into four groups based on their weight gain during follow-up: < 0 kg, 0–1.9 kg, 2.0–3.9 kg, and ≥ 4.0 kg. Cox proportional hazard models, adjusted for various variables, were used to estimate hazard ratios (HRs) for the association between post-cessation weight gain and incident T2DM in NAFLD and NAFLD-free individuals.

Results At baseline, we included 1,409 NAFLD and 5150 NAFLD-free individuals. During a total of 39,259 person-years of follow-up, 222 (15.8%) NAFLD patients and 621 (12.1%) NAFLD-free participants quit smoking, with the corresponding means (standard deviations) of post-cessation weight gain being 2.24 (3.26) kg and 1.15 (3.51) kg, respectively. Among NAFLD individuals, compared to current smokers, the fully adjusted HRs (95% CI) for incident T2DM were 0.41 (0.06–3.01), 2.39 (1.21–4.70), 4.48 (2.63–7.63), and 6.42 (3.68–11.23) for quitters with weight gains < 0 kg, 0.0–1.9 kg, 2.0–3.9 kg, and ≥ 4.0 kg, respectively. For NAFLD-free individuals, we only observed a significant association between post-cessation weight gain ≥ 4.0 kg and the risk of incident T2DM ($P < 0.001$). Further analysis revealed that the impact of post-cessation weight gain on T2DM risk was not affected by alcohol consumption or obesity status at baseline.

Conclusions Mild post-cessation weight gain significantly increased the risk of T2DM in male NAFLD patients but not in male NAFLD-free individuals. Therefore, it is recommended that individuals with NAFLD manage their weight after quitting smoking.

Keywords Nonalcoholic fatty liver disease, Type 2 diabetes, Smoking cessation, Weight gain

*Correspondence:
Chengfu Xu
xiaofu@zju.edu.cn
Lei Xu
xulei22@163.com
Full list of author information is available at the end of the article

Introduction

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the most common chronic liver disease, with a global prevalence of 38% [1]. NAFLD often precedes type 2 diabetes mellitus (T2DM) [2], which is one of the most significant extrahepatic complications [3, 4]. Considering that there are no approved pharmacological treatments, lifestyle modification is necessary but challenging to reduce the risk of T2DM in patients with NAFLD [5].

Cigarette smoking has a significant negative impact on public health, causing over 480,000 deaths each year [6, 7]. Smoking has been reported as a risk factor for NAFLD and may accelerate the progression of liver disease [8–10]. Therefore, smoking cessation is recommended for NAFLD patients [11, 12]. However, smoking cessation can be complicated by weight gain [13], which typically occurs within 5–7 years after quitting smoking [14, 15]. Post-cessation weight gain poses a potential health concern, especially in NAFLD patients [16]. Weight gain is an important risk factor for the development of T2DM in NAFLD patients [17, 18]. To date, clinical evidence about the impact of post-cessation weight gain on NAFLD and its comorbidities remains limited [19]. Furthermore, post-cessation weight gain limits the willingness of patients and reduces the success of cessation attempts. It has been reported to be a significant cause of relapse [20]. Therefore, it is important to assess the impact of weight change after smoking cessation on patients with NAFLD. Appropriate management of post-cessation weight could maximize its health benefits.

In this large-scale cohort study, we aimed to assess the effects of smoking cessation and subsequent weight change on the risk of incident T2DM in NAFLD and NAFLD-free smokers. These findings will facilitate the provision of smoking cessation advice to patients with NAFLD in clinical practice.

Methods

Study population

The study population was composed of adults aged ≥ 18 years who attended annual health checkups at Zhenhai Lianhua Hospital in 2007. Due to the low proportion of female smokers in China, we included only males in this study. We excluded the following participants: (i) female subjects (ii) those with missing information on hepatic ultrasound, smoking status, or body weight and (iii) those with excess alcohol intake or a history of chronic liver disease at baseline, including viral hepatitis (such as hepatitis B and hepatitis C), drug-induced liver disease, autoimmune liver disease, and genetic metabolic liver diseases (such as Wilson's disease). During the follow-up, we further excluded the following participants: (i) those who were diagnosed with T2DM at baseline and (ii) those who were lost to follow-up. After the exclusions, a total of 6,559 participants were included for follow-up until December 2014 (Supplementary Figure S1). Previous studies have shown that weight gain from smoking cessation usually occurs within 5–7 years after smoking cessation [14, 15]. Longer follow-up periods may increase the potential bias for weight gain due to other causes. Thus, we set the follow-up endpoint at the end of 2014 to minimize potential bias in weight gain due to other factors.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University (Approval Number: 2022RS127). The data utilized in this study were obtained from previous medical records. The waiver of informed consent was approved by the Hospital Ethics Committee, as it was determined that this waiver would not adversely affect the rights and health of the subjects. The study was registered with ClinicalTrials.gov (Registration Number: NCT05550688).

Assessment of smoking status and weight change

For each year of follow-up, we identified participants who reported being smokers in the previous year but non-smokers in the current year as recent quitters and considered the current year as the start of smoking cessation.

We calculated the duration of smoking cessation from the start of quitting to the time of relapse, the onset of T2DM, or the end of follow-up. Participants were divided into four groups based on their body weight changes during follow-up: < 0 kg, 0–1.9 kg, 2.0–3.9 kg, and ≥ 4.0 kg. Participants were divided into four groups according to the relative percentage of weight change: < 0%, 0.0–2.9%, 3.0–5.9%, and ≥ 6.0%, respectively, in NAFLD patients. We further assessed the association between the relative percentage of weight change after quitting smoking and the risk of incident T2DM. Additionally, transient quitters were defined as those who reported being non-smokers in the current year but were current smokers in the previous year and next year.

Assessment of demographic and clinical characteristics

Blood samples were measured using an autoanalyzer [21]. Standing height without shoes and body weight in light clothing were measured according to our previous procedure [21]. Blood pressure was determined by an automatic sphygmomanometer while participants were in a resting state. All participants were examined in the morning after fasting overnight.

Diagnosis of NAFLD and T2DM

We diagnosed NAFLD based on abdominal ultrasonography according to the Chinese Liver Disease Association [22]. Abdominal ultrasonography was performed by experienced ultrasonographers [21]. T2DM was defined as individuals with fasting plasma glucose ≥ 126 mg/dl, an HbA1c ≥ 6.5%, or self-reported clinician-diagnosed T2DM [23].

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and were analyzed by one-way ANOVA or Student's *t* test. Categorical variables are expressed as percentages (numbers) and were analyzed using Pearson's chi-squared test.

Cox proportional hazards models were applied to assess the associations of weight change during smoking cessation with the risk of T2DM. The proportional hazards assumption was tested using Schoenfeld residuals. No evidence of violation of the proportional hazards assumption was found. In multivariable models, we constructed three nested models for analysis: (i) Model 1 adjusted for age and body mass index (ii) Model 2, Model 1 plus drinking status and (iii) Model 3, Model 2 plus aspartate aminotransferase, total cholesterol, triacylglycerol, creatinine, albumin, and systolic blood pressure. In the fully adjusted model, we further explored the interaction effect of NAFLD status on the association between smoking cessation and T2DM by fitting an interaction term on a multiplicative scale.

To test the robustness of our findings, we performed three sensitivity analyses: (i) considering the possible synergistic effect of obesity and NAFLD, we further explored the relationship between weight gain after smoking cessation and the risk of T2DM incidence in non-obese individuals at baseline (ii) to reduce the bias of relapse after cessation, we repeated the analysis after removing 376 individuals who relapsed into smoking cigarettes during follow-up and (iii) previous studies and our results evaluated the trajectory of weight change after quitting smoking, with weight gain occurring primarily in the first 2 years after quitting smoking [14]. Thus, we further evaluated the relationship between weight change in the first and second years after smoking cessation and the incidence of T2DM.

Statistical analyses were performed using R version 3.5.1 (The R Foundation for Statistical Computing). *P* values were two-tailed, and statistical significance was set at $P < 0.05$.

Results

Clinical characteristics of the study subjects

A total of 6,559 male participants (5150 NAFLD-free individuals and 1,409 NAFLD patients) were included in the cohort analysis at baseline (Supplementary Figure S1). Participants were divided into current smokers and non-smokers according to their baseline smoking status. The clinical characteristics are summarized according to NAFLD status and smoking status in Table 1. Smokers had a greater body mass index, waist circumference, and serum levels of total cholesterol and triglycerides in both NAFLD and NAFLD-free individuals (all $P < 0.05$), indicating that smoking may be associated with more unfavorable metabolic profiles than non-smokers.

Follow-up outcomes

During a total of 39,259 person-years of follow-up, 222 (15.8%) NAFLD patients and 621 (12.1%) NAFLD-free participants quit smoking. The clinical characteristics are summarized according to smoking status changes during follow-up in Supplementary Table S1. Compared with current smokers, recent quitters were older in both NAFLD and NAFLD-free individuals (both with $P < 0.05$).

During the follow-up, 363 cases of T2DM were identified (Supplementary Table S2). Compared with participants who did not develop T2DM, those who developed T2DM were older and had greater body mass index and serum triglyceride levels (all with $P < 0.05$). Notably, smoking was significantly associated with an increased risk of incident T2DM in both NAFLD and NAFLD-free populations (both with $P < 0.001$ Supplementary Table S3).

Smoking cessation and risk of incident T2DM

The significant association between smoking and an elevated risk of incident T2DM prompted us to investigate whether quitting smoking decreases this risk. Table 2 shows the association between smoking cessation and the risk of incident T2DM among the whole study population. Surprisingly, we found that smoking cessation was significantly associated with an increased risk of incident T2DM compared with current smokers, after adjusting for age, body mass index, drinking status, aspartate aminotransferase, total cholesterol, triacylglycerol, creatinine, albumin, and systolic blood pressure (Fig. 1). The fully adjusted hazard ratio (HR) (95% confidence interval [CI]) for incident T2DM was 2.16 (95% CI 1.67–2.80).

Because NAFLD is a major risk factor for T2DM, we separately analyzed the association between smoking cessation and the risk of incident T2DM in NAFLD and NAFLD-free participants (Fig. 1). We found that

Table 1 Baseline characteristics of the follow-up population with/without NAFLD stratified by smoking status

Variables	Overall ($n=6559$)	Participants with NAFLD ($n=1409$)			Participants without NAFLD ($n=5150$)		
		Smokers ($n=754$)	Non-smokers ($n=655$)	*P* value	Smokers ($n=2382$)	Non-smokers ($n=2768$)	*P* value
Age, year	44.78 (12.67)	45.40 (10.55)	47.89 (13.42)	< 0.001	44.28 (10.62)	44.32 (14.42)	0.913
Current drinker (%)	1791 (27.3)	274 (36.4)	116 (17.7)	< 0.001	924 (38.8)	477 (17.2)	< 0.001
Body mass index, kg/m^2	23.57 (3.02)	26.32 (2.97)	26.11 (2.62)	0.167	22.78 (2.66)	22.89 (2.62)	0.155
Waist circumference, cm	82.13 (8.32)	89.72 (6.90)	88.59 (7.44)	0.003	80.28 (7.41)	80.14 (7.64)	0.491
Aspartate aminotransferase, U/L	25.00 [20.00, 30.00]	30.00 [23.00, 40.00]	30.00 [24.00, 37.00]	0.892	23.00 [20.00, 29.00]	24.00 [20.00, 28.00]	0.116
Total cholesterol, mmol /L	5.10 (0.99)	5.55 (1.04)	5.41 (1.02)	0.007	5.05 (0.96)	4.96 (0.93)	< 0.001
Triglyceride, mmol/L	1.73 [1.21, 2.57]	2.67 [1.86, 3.74]	2.41 [1.67, 3.21]	< 0.001	1.67 [1.18, 2.35]	1.52 [1.09, 2.16]	< 0.001
Creatinine, umol/L	72.51 (18.83)	71.28 (10.22)	72.74 (10.97)	0.010	71.90 (10.24)	73.33 (26.31)	0.013
Albumin, g/L	45.18 (2.14)	45.26 (2.09)	45.59 (2.00)	0.002	44.92 (2.10)	45.29 (2.19)	< 0.001
White blood cell, $\times 10^9$/L	6.55 (1.75)	7.24 (1.66)	6.76 (1.46)	< 0.001	6.77 (2.10)	6.13 (1.34)	< 0.001
Hemoglobin, g/L	144.30 (9.08)	147.34 (8.74)	146.09 (9.03)	0.009	144.41 (8.95)	142.95 (9.03)	< 0.001
Platelet count, $\times 10^9$/L	199.17 (49.98)	207.42 (49.41)	205.82 (50.32)	0.548	200.05 (52.66)	194.59 (47.13)	< 0.001
Systolic blood pressure, mmHg	124.53 (14.06)	129.33 (14.13)	131.91 (14.27)	0.001	121.50 (13.27)	124.09 (13.69)	< 0.001
Diastolic blood pressure, mmHg	78.59 (9.79)	83.16 (9.44)	83.85 (9.53)	0.172	76.94 (9.68)	77.53 (9.22)	0.025
Fasting blood glucose, mmol/L	4.71 (0.58)	4.84 (0.63)	4.88 (0.60)	0.224	4.61 (0.57)	4.72 (0.55)	< 0.001

NAFLD nonalcoholic fatty liver disease

smoking cessation was significantly associated with an increased risk of incident T2DM in NAFLD patients but not in NAFLD-free individuals. The fully adjusted HRs (95% CIs) were 3.23 (2.21–4.74) and 1.30 (0.89–1.90) in NAFLD- and NAFLD-free individuals, respectively. Although the explanation remains unclear, the above findings clearly illustrated that NAFLD patients and NAFLD-free individuals had different risks of incident T2DM after smoking cessation ($P_{\text{interaction}} < 0.001$).

Post-cessation weight gain and risk of incident T2DM

Since 58.0% of recent quitters had less than 5 years of follow-up, we assessed the mean cumulative weight gain by smoking cessation duration in the first 4 years. As shown in Supplementary Figure S2, recent quitters experienced a mean weight gain of 0.74 kg in the first year and 1.21 kg in the second year after quitting smoking. Compared with those in current smokers and never-smokers or ex-smokers, weight changes were greatest in recent quitters during the first and second years of follow-up ($P < 0.001$). These results indicate that individuals who quit smoking showed significantly greater weight gain than did current smokers, never-smokers, or former smokers. The detailed weight changes during the first and second years of follow-up are illustrated in the Sankey diagram (Supplementary Figure S3).

Furthermore, we found that participants with NAFLD experienced greater weight gain after smoking cessation than did those without NAFLD during the follow-up period (2.28 [3.35] kg versus 1.19 [3.37] kg, $P < 0.001$). As shown in Table 2, compared to current smokers, recent quitters with weight gains of 0–1.9 kg, 2.0–3.9 kg, and ≥ 4.0 kg had a significantly greater risk of incident T2DM among individuals with NAFLD, and the corresponding fully adjusted HRs (95% CIs) were 0.41 (0.06–3.01), 2.39 (1.21–4.70), 4.48 (2.63–7.63), and 6.42 (3.68–11.23), respectively. This indicates that even mild weight gain after smoking cessation significantly increases the risk of T2DM in NAFLD patients.

In addition, we noted a significantly greater risk of T2DM among transient quitters than among current smokers in the fully adjusted model ($P < 0.001$). This suggests that short periods of smoking cessation may still increase the risk of developing diabetes. Short-term quitters gained more weight after quitting than

Table 2 Association between smoking cessation and the incidence of T2DM among individuals by smoking status

	Cases/Person–year	Univariate analysis	Multivariable–adjusted HR (95% CI)		
		HR (95% CI)	Model 1	Model 2	Model 3
For NAFLD individuals					
Current smokers	43/2,458	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Recent quitters					
< 0 kg	1/158	0.40 (0.05–2.88)	0.41 (0.06–2.98)	0.41 (0.06–3.00)	0.41 (0.06–3.01)
0.0–1.9 kg	11/261	2.67 (1.36–5.23)**	2.33 (1.19–4.58)*	2.32 (1.18–4.54)*	2.39 (1.21–4.70)*
2.0–3.9 kg	22/281	5.05 (2.98–8.53)***	4.37 (2.57–7.43)***	4.38 (2.58–7.45)***	4.48 (2.63–7.63)***
≥ 4.0 kg	19/219	5.63 (3.24–9.77)***	6.17 (3.55–10.73)***	6.03 (3.46–10.53)***	6.42 (3.68–11.23)***
Transient quitters	31/687	2.75 (1.73–4.39)***	2.85 (1.79–4.54)***	2.91 (1.82–4.64)***	2.84 (1.77–4.55)***
Never smokers or ex–smokers	44/4,186	0.60 (0.39–0.91)*	0.50 (0.32–0.76)**	0.51 (0.33–0.78)**	0.49 (0.32–0.77)**
For NAFLD–free individuals					
Current smokers	75/9,730	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Recent quitters					
< 0 kg	6/898	0.79 (0.34–1.81)	0.57 (0.25–1.33)	0.59 (0.26–1.36)	0.63 (0.27–1.45)
0.0–1.9 kg	6/612	1.16 (0.50–2.67)	0.88 (0.38–2.04)	0.86 (0.37–1.98)	0.87 (0.38–2.01)
2.0–3.9 kg	6/490	1.45 (0.63–3.34)	1.47 (0.64–3.39)	1.49 (0.65–3.43)	1.54 (0.66–3.56)
≥ 4.0 kg	13/573	2.71 (1.50–4.90)***	2.56 (1.42–4.62)**	2.50 (1.38–4.53)**	2.80 (1.54–5.07)***
Transient quitters	14/1,050	1.55 (0.88–2.76)	1.39 (0.78–2.47)	1.42 (0.80–2.52)	1.44 (0.81–2.56)
Never smokers or ex–smokers	72/17,656	0.53 (0.38–0.73)***	0.40 (0.28–0.56)***	0.43 (0.30–0.60)***	0.42 (0.30–0.59)***
For total individuals					
Current smokers	118/12,188	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Recent quitters					
< 0 kg	7/1,056	0.67 (0.31–1.45)	0.57 (0.26–1.23)	0.58 (0.27–1.25)	0.60 (0.28–1.30)
0.0–1.9 kg	17/873	1.99 (1.19–3.32)**	1.57 (0.94–2.62)	1.53 (0.92–2.56)	1.50 (0.90–2.50)
2.0–3.9 kg	28/771	3.74 (2.47–5.66)***	3.30 (2.17–5.01)***	3.33 (2.19–5.05)***	3.23 (2.13–4.91)***
≥ 4.0 kg	32/792	4.17 (2.81–6.19)***	4.16 (2.80–6.17)***	4.03 (2.72–6.00)***	4.14 (2.77–6.18)***
Transient quitters	45/1,737	2.64 (1.87–3.73)***	2.37 (1.68–3.36)***	2.42 (1.71–3.42)***	2.22 (1.57–3.16)***
Never smokers or ex–smokers	116/21,842	0.55 (0.42–0.71)***	0.44 (0.34–0.58)***	0.46 (0.36–0.61)***	0.45 (0.34–0.59)***

HRs (95% CI) were estimated with the use of a Cox proportional–hazards model. Model 1: adjusted for age, and body mass index. Model 2: adjusted for model 1 plus drinking status. Model 3: adjusted for model 2 plus aspartate aminotransferase, total cholesterol, triacylglycerol, creatinine, albumin, and systolic blood pressure. All data are expressed as Hazard ratios with 95% confidence interval with the use of a Cox proportional–hazards model

CI confidence interval, *HR* hazard ratio, *NAFLD* nonalcoholic fatty liver disease, *T2DM* type 2 diabetes

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

did continued smokers (0.29 [2.74] versus 0.19 [2.82] in the first year). This further suggested the importance of weight control after smoking cessation.

For NAFLD-free individuals, the fully adjusted HRs (95% CI) for the risk of T2DM were 0.63 (0.27–1.45), 0.87 (0.38–2.01), and 1.54 (0.66–3.56) among recent quitters with weight changes < 0 kg, 0.0–1.9 kg and 2.0–3.9 kg, respectively. We only observed a significant association between ≥ 4.0 kg weight gain after smoking cessation and the risk of T2DM, with a fully adjusted HR (95% CI) of 2.80 (1.54–5.07) (Table 2). This result suggested that mild post-cessation weight gain does not significantly increase the risk of T2DM in NAFLD-free participants.

We further assessed the association between the relative percentage of weight change after quitting smoking and the risk of incident T2DM (Fig. 2). Compared with those of current smokers, the fully adjusted HRs (95% CIs) for incident T2DM were 0.41 (0.06–3.00), 2.23 (1.16–4.28), 5.32 (3.23–8.78), and 6.47 (3.43–12.24) among recent quitters with weight gain < 0%, 0.0–2.9%, 3.0–5.9%, and ≥ 6.0%, respectively, among NAFLD patients. Among NAFLD-free individuals, we only observed a significant association between ≥ 6% weight gain after smoking cessation and the risk of T2DM ($P = 0.010$). This further confirmed that mild post-cessation weight gain was associated with an increased risk of incident T2DM in NAFLD patients but not in NAFLD-free participants.

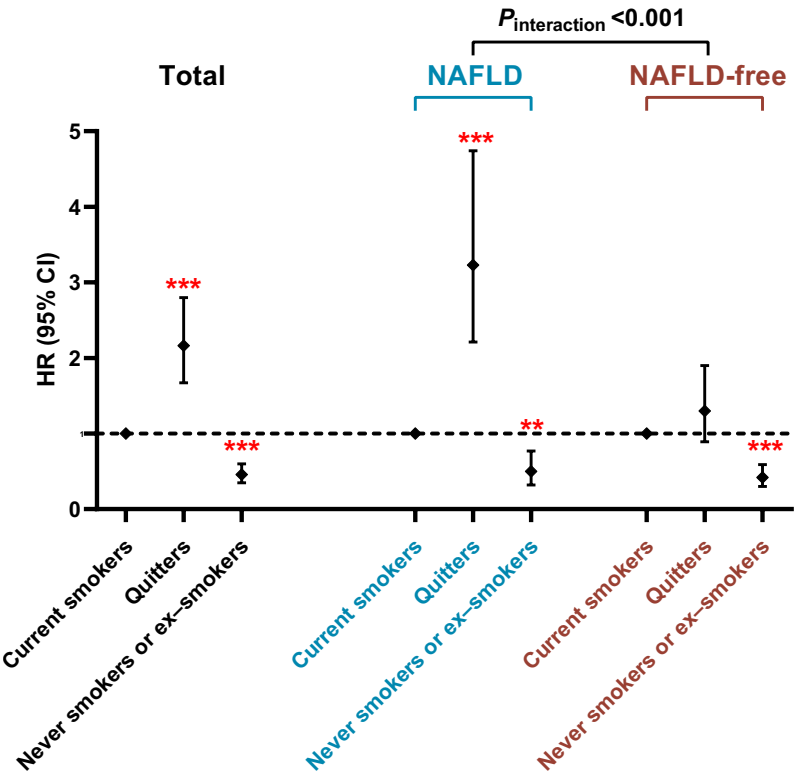


Fig. 1 The interaction effect of NAFLD status on the association between smoking cessation and T2DM. *CI* confidence interval, *HR* hazard ratio, *NAFLD* nonalcoholic fatty liver disease, *T2DM* type 2 diabetes. The Cox proportional hazards model was adjusted for age, body mass index, drinking status, aspartate aminotransferase, total cholesterol, triacylglycerol, creatinine, albumin, and systolic blood pressure. $^{**}P < 0.01$, $^{***}P < 0.001$

Sensitivity analyses

To assess the robustness of our findings, we conducted three sensitivity analyses:

First, we explored the association between post-cessation weight gain and the risk of T2DM in non-drinkers and non-obese individuals and observed that the impact of weight gain after smoking cessation was not modified by alcohol consumption or obesity status (Fig. 3A, B).

Second, to minimize the potential impact of smoking relapse, we removed participants who relapsed smoking during follow-up (Supplementary Table S4). Compared with those of current smokers, the fully adjusted HRs (95% CIs) for incident T2DM were 1.00 (0.14–7.30), 3.23 (1.55–6.75), 5.04 (2.69–9.44), and 7.05 (4.04–12.30) for recent quitters with weight gains < 0 kg, 0–1.9 kg, 2.0–3.9 kg, and ≥ 4.0 kg, respectively, among individuals with NAFLD. For NAFLD-free individuals, the corresponding HRs (95% CI) were 0.82 (0.30–2.27), 1.53 (0.61–3.80), 2.50 (0.91–6.88), and 3.60 (1.72–7.55).

Third, we evaluated the relationship between weight change in the first and second years after quitting smoking and the incidence of T2DM (Supplementary Figure S4). We obtained similar results regarding the effect of weight change during the first year after smoking cessation on NAFLD individuals. Compared with those of current smokers, we observed fully adjusted HRs (95% CIs) for incident T2DM of 1.27 (0.57–2.87), 3.98 (2.26–7.02), 4.77 (2.64–8.60), and 7.16 (3.69–13.91) for recent quitters with weight gains < 0 kg, 0–1.9 kg, 2.0–3.9 kg, and ≥ 4.0 kg, respectively, among NAFLD patients. We found a significant relationship between weight gain ≥ 4.0 kg after smoking cessation and T2DM risk ($P < 0.001$) among NAFLD-free individuals. Similar associations were observed after removing 86 individuals with only 1 year of follow-up (Supplementary Figure S4).

Overall, these sensitivity analyses confirm the robustness of our findings and provide further evidence for the significant association between post-cessation weight gain and T2DM risk in NAFLD patients but not in NAFLD-free individuals.

Discussion

This cohort study provides novel insight into the differential impact of post-cessation weight gain on the risk of incident T2DM in individuals with and without NAFLD. Our findings revealed that even mild weight gain following smoking cessation is significantly associated

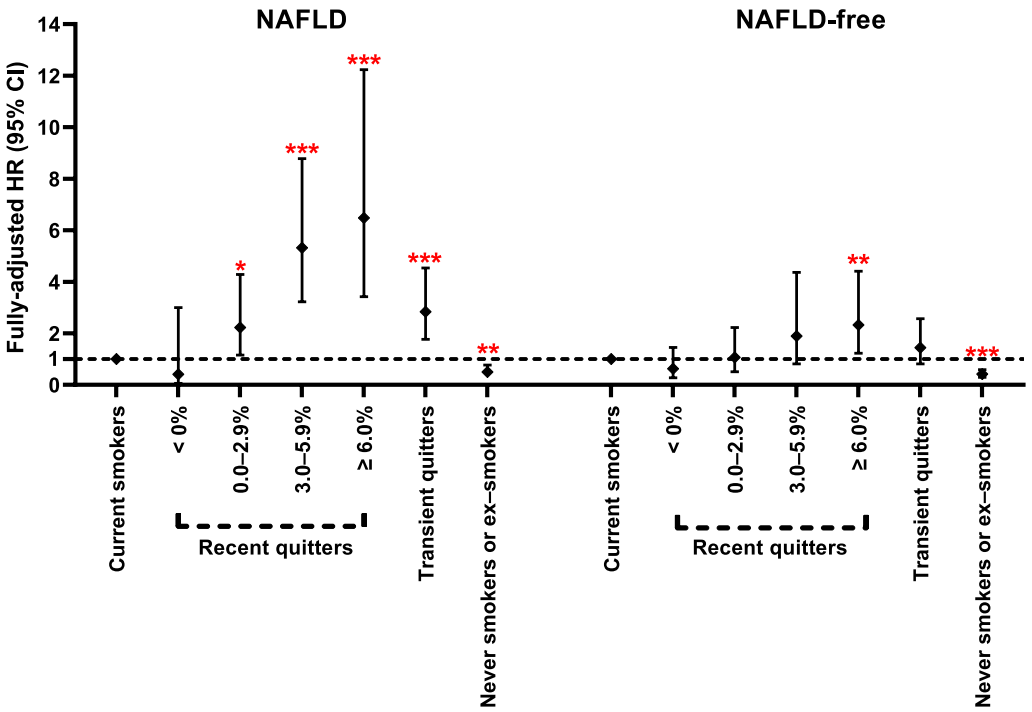
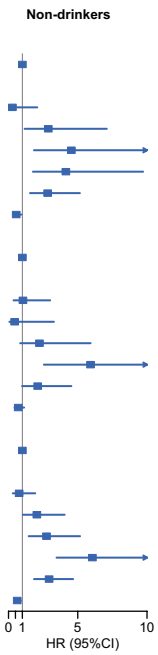


Fig. 2 Association between the relative percentage of weight change after quitting smoking and the risk of T2DM in the fully adjusted multivariable model. *CI* confidence interval, *HR* hazard ratio, *NAFLD* nonalcoholic fatty liver disease, *T2DM* type 2 diabetes. The Cox proportional hazards model was adjusted for age, body mass index, drinking status, aspartate aminotransferase, total cholesterol, triacylglycerol, creatinine, albumin, and systolic blood pressure. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

A Non-drinkers

	Hazard ratio (95% CI)
For NAFLD individuals	
Current smokers	1.00 (reference)
Recent quitters	
- <0 kg	0.28 (0.04 to 2.07)
- 0.0-1.9 kg	2.87 (1.16 to 7.10)*
- 2.0-3.9 kg	4.54 (1.84 to 11.21)**
- ≥4.0 kg	4.14 (1.76 to 9.72)**
Transient quitters	2.83 (1.55 to 5.15)***
Never smokers or ex-smokers	0.55 (0.33 to 0.93)*
For NAFLD-free individuals	
Current smokers	1.00 (reference)
Recent quitters	
- <0 kg	1.04 (0.36 to 3.01)
- 0.0-1.9 kg	0.44 (0.06 to 3.28)
- 2.0-3.9 kg	2.23 (0.84 to 5.93)
- ≥4.0 kg	5.92 (2.55 to 13.74)***
Transient quitters	2.11 (0.98 to 4.54)
Never smokers or ex-smokers	0.70 (0.44 to 1.13)
For total individuals	
Current smokers	1.00 (reference)
Recent quitters	
- <0 kg	0.77 (0.31 to 1.93)
- 0.0-1.9 kg	2.05 (1.03 to 4.05)*
- 2.0-3.9 kg	2.74 (1.46 to 5.17)**
- ≥4.0 kg	6.06 (3.47 to 10.58)***
Transient quitters	2.93 (1.84 to 4.67)***
Never smokers or ex-smokers	0.63 (0.45 to 0.89)**



B Non-obese individuals

	Hazard ratio (95% CI)
For NAFLD individuals	
Current smokers	1.00 (reference)
Recent quitters	
- <0 kg	0.29 (0.04 to 2.11)
- 0.0-1.9 kg	3.47 (1.67 to 7.23)***
- 2.0-3.9 kg	6.30 (3.27 to 12.14)***
- ≥4.0 kg	2.90 (1.19 to 7.07)*
Transient quitters	2.41 (1.36 to 4.26)**
Never smokers or ex-smokers	0.44 (0.26 to 0.74)**
For NAFLD-free individuals	
Current smokers	1.00 (reference)
Recent quitters	
- <0 kg	0.34 (0.11 to 1.08)
- 0.0-1.9 kg	0.62 (0.22 to 1.70)
- 2.0-3.9 kg	1.48 (0.71 to 3.10)
- ≥4.0 kg	3.03 (1.50 to 6.09)**
Transient quitters	1.47 (0.82 to 2.62)
Never smokers or ex-smokers	0.42 (0.29 to 0.60)***
For total individuals	
Current smokers	1.00 (reference)
Recent quitters	
- <0 kg	0.57 (0.25 to 1.31)
- 0.0-1.9 kg	1.51 (0.88 to 2.57)
- 2.0-3.9 kg	2.54 (1.56 to 4.14)***
- ≥4.0 kg	3.92 (2.52 to 6.10)***
Transient quitters	1.97 (1.32 to 2.91)***
Never smokers or ex-smokers	0.43 (0.32 to 0.58)***

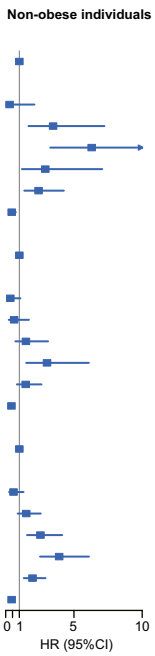


Fig. 3 Sensitivity analyses of the association between smoking cessation and the incidence of T2DM by smoking status in a fully adjusted model. **A** Among individuals who reported no alcohol consumption at baseline. **B** Among individuals with a baseline BMI < 28 kg/m^2. *CI* confidence interval, *NAFLD* nonalcoholic fatty liver disease. The Cox proportional hazards model was adjusted for age, body mass index, drinking status, aspartate aminotransferase, total cholesterol, triacylglycerol, creatinine, albumin, and systolic blood pressure. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

with an increased risk of T2DM in individuals with NAFLD. In NAFLD-free individuals, this risk becomes apparent only when weight gain exceeds 4.0 kg. These results underscore the unique vulnerability of NAFLD patients to weight gain-related metabolic disturbances after smoking cessation. Furthermore, the sensitivity analyses confirmed the robustness of these findings in subgroups of non-drinkers and non-obese individuals. These observations highlight the critical importance of managing weight gain post-cessation, particularly in NAFLD patients, to mitigate the elevated risk of T2DM and optimize health outcomes.

Smoking is an independent risk factor for NAFLD progression [8, 9]. Jung et al. performed a cohort study of 199,468 Korean adults [9] and reported that current smoking status, pack-years, and urinary cotinine levels were positively associated with the risk of incident NAFLD. Therefore, it is advised that patients with NAFLD quit smoking. Smoking cessation is a common clinical problem. As part of the "Healthy China 2030" initiative, the Chinese government aims to reduce smoking prevalence from 27.7 to 20% by 2030 [24], which means a net reduction of nearly 100 million smokers [25]. However, smoking cessation is often accompanied by weight gain [26], which could be a potential risk factor for NAFLD progression. The magnitude of economic and medical costs associated with incident T2DM in individuals with NAFLD is significant. A better understanding of the impact of smoking cessation on NAFLD may provide new insights into NAFLD pathogenesis and develop preventive strategies.

Previous studies have shown that weight gain after smoking cessation is considered acceptable since it is not associated with an increased risk of cardiovascular disease or chronic diseases [27, 28]. However, our study provides novel and critical insight into the impact of weight gain on the risk of developing T2DM in both NAFLD and NAFLD-free populations. Specifically, we found that even mild weight gain during follow-up after smoking cessation significantly increased the risk of T2DM in individuals with NAFLD. In contrast, for NAFLD-free individuals, an increased risk of T2DM was observed only if they weighed more than 4.0 kg. This critical finding underscores the importance of managing weight gain after smoking cessation, particularly in NAFLD patients, to mitigate the heightened risk of T2DM.

Relapse to smoking after quitting smoking is common among people who have quit smoking [29]. Therefore, we excluded the relapsed smoking population from the sensitivity analysis and again assessed the correlation. In this analysis, we likewise observed a similar phenomenon. These robust results suggest that patients with NAFLD need strict weight control after smoking cessation to reduce the risk of developing T2DM.

Two strengths of this study are the large sample size and its cohort design. Additionally, our study included repeated measures of smoking status during follow-up instead of depending on the "point prevalence" of smoking cessation, which could reflect dynamic changes in smoking status. We further excluded the relapsed smoking population from our sensitivity analysis as mentioned above. The results of these analyses provide evidence for further refining cessation management.

There are some limitations that should be acknowledged. First, our study focused on the Chinese population that regularly underwent health examinations. This may limit the generalizability of our results to other ethnic populations. Second, some additional factors, such as socioeconomic status, physical activity levels, and dietary habits, were not fully adjusted due to the lack of corresponding data. This may have led to residual confounders. Third, female participants were not included in our analysis since female smokers represent a very small minority in Chinese society [30]. The current smoking prevalence was only 2.1% in 2018 [30]. Future studies could include female participants to provide a more comprehensive understanding of the relationship between smoking cessation and type 2 diabetes risk. Fourth, fatty liver was diagnosed by ultrasonographic methods in our study. Although liver biopsy is the gold standard, it is difficult and impractical to perform in community-based studies. The ultrasound definition of steatosis is used in the current guidelines in China [22]. Additionally, since this study was conducted before the introduction of the MASLD definition, we adopted the NAFLD definition for fatty liver. However, according to recent literature, the differences between MASLD and NAFLD are minimal, suggesting that findings based on the NAFLD definition remain applicable and valid under the new MASLD framework [31]. Finally, reliance on self-reported smoking status may introduce bias or misclassification, despite the use of trained nurses to conduct professional and consistent interviews.

In conclusion, this large cohort study indicated that even mild weight gain during follow-up after smoking cessation is significantly associated with an increased risk of T2DM in male individuals with NAFLD. This finding emphasized the importance of weight control after smoking cessation to reduce the potential risk of T2DM, especially in individuals with NAFLD.

Abbreviations

CI Confidence interval

HR	Hazard ratio
NAFLD	Nonalcoholic fatty liver disease
T2DM	Type 2 diabetes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01435-4.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Acknowledgements
The authors thank all the staff and participants of this study for their important contributions.

Author contributions
Study concept and design: L. Xu, C. Xu, C. Yu, and J. Xie; acquisition of data: P. Lin, L. Hou, and M. Miao; analysis and interpretation of the data: P. Lin, L. Hou, Z. Zhu, and Y. Li; drafting of the manuscript: J. Xie and P. Lin; critical revision of the manuscript: L. Xu, C. Xu, and C. Yu; obtained funding; C. Xu, L. Xu, and J. Xie; study supervision: L. Xu, C. Xu, C. Yu, and Y. Li.

Funding
This work was supported by the National Natural Science Foundation of China (82300654, 82270602, 82270597, 82070585, and U20A20347), the Key Research and Development Program of Zhejiang Province (2024C03153), the Ningbo Top Medical and Health Research Program (No. 2023020612), the project of Ningbo leading Medical & Health Discipline (2022-S04), and the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2023KY257).

Availability of data and materials
The data that support the findings of this study are available from the corresponding authors, Dr. Lei Xu and Dr. Chengfu Xu, upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University (Approval Number: 2022RS127). The study was registered with ClinicalTrials.gov (Registration Number: NCT05550688).

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Gastroenterology, the First Affiliated Hospital of Ningbo University, No. 59 Liuting Street, Haishu District, Ningbo 315000, China. [2]Department of Gastroenterology, the First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, China. [3]Zhejiang Provincial Clinical Research Center for Digestive Diseases, Hangzhou, China. [4]Department of Internal Medicine, Zhenhai Lianhua Hospital, Ningbo, China.

Received: 4 June 2024 Accepted: 31 July 2024
Published online: 08 August 2024

References

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77(4):1335–47.
2. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. Nat Rev Gastroenterol Hepatol. 2017;14(1):32–42.
3. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol. 2022;10(4):284–96.
4. Huang HLZ, Xu M, Chen Y, Xu C. Global burden trends of MAFLD-related liver cancer from 1990 to 2019. Portal Hypertens Cirrhosis. 2023;2:127–35.
5. Zhang C, Yang M. Current options and future directions for NAFLD and NASH treatment. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22147571.
6. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the Surgeon General. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US) 2014.
7. Akhavan Rezayat A, Dadgar Moghadam M, Ghasemi Nour M, Shirazinia M, Ghodsi H, Rouhbakhsh Zahmatkesh MR, et al. Association between smoking and non-alcoholic fatty liver disease: a systematic review and meta-analysis. SAGE Open Med. 2018;6:2050312117745223.
8. Azzalini L, Ferrer E, Ramalho LN, Moreno M, Domínguez M, Colmenero J, et al. Cigarette smoking exacerbates nonalcoholic fatty liver disease in obese rats. Hepatology. 2010;51(5):1567–76.
9. Jung HS, Chang Y, Kwon MJ, Sung E, Yun KE, Cho YK, et al. Smoking and the risk of non-alcoholic fatty liver disease: a cohort study. Am J Gastroenterol. 2019;114(3):453–63.
10. Kim NH, Jung YS, Hong HP, Park JH, Kim HJ, Park DI, et al. Association between cotinine-verified smoking status and risk of nonalcoholic fatty liver disease. Liver Int. 2018;38(8):1487–94.
11. Marti-Aguado D, Clemente-Sanchez A, Bataller R. Cigarette smoking and liver diseases. J Hepatol. 2022;77(1):191–205.
12. Addolorato G, Bataller R, Burra P, DiMartini A, Graziadei I, Lucey MR, et al. Liver transplantation for alcoholic liver disease. Transplantation. 2016;100(5):981–7.
13. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ. 2012;345:e4439.
14. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. N Engl J Med. 2018;379(7):623–32.
15. Liu G, Hu Y, Zong G, Pan A, Manson JE, Rexrode KM, et al. Smoking cessation and weight change in relation to cardiovascular disease incidence and mortality in people with type 2 diabetes: a population-based cohort study. Lancet Diabetes Endocrinol. 2020;8(2):125–33.
16. Takenaka H, Fujita T, Masuda A, Yano Y, Watanabe A, Kodama Y. Non-alcoholic fatty liver disease is strongly associated with smoking status and is improved by smoking cessation in Japanese males: a retrospective study. Kobe J Med Sci. 2020;66(3):E102–12.
17. Xue M, Yang X, Zou Y, Liu T, Su Y, Li C, et al. A non-invasive prediction model for non-alcoholic fatty liver disease in adults with type 2 diabetes based on the population of northern Urumqi. China Diabetes Metab Syndr Obes. 2021;14:443–54.
18. Rodriguez LA, Kanaya AM, Shiboski SC, Fernandez A, Herrington D, Ding J, et al. Does NAFLD mediate the relationship between obesity and type 2 diabetes risk? Evidence from the multi-ethnic study of atherosclerosis (MESA). Ann Epidemiol. 2021;63:15–21.
19. Lange NF, Radu P, Dufour JF. Prevention of NAFLD-associated HCC: Role of lifestyle and chemoprevention. J Hepatol. 2021;75(5):1217–27.
20. Levine MD, Bush T, Magnusson B, Cheng Y, Chen X. Smoking-related weight concerns and obesity: differences among normal weight, overweight, and obese smokers using a telephone tobacco quitline. Nicotine Tob Res. 2013;15(6):1136–40.
21. Xu L, Xie J, Chen S, Chen Y, Yang H, Miao M, et al. Light-to-moderate alcohol consumption is associated with increased risk of type 2 diabetes in individuals with nonalcoholic fatty liver disease: a nine-year cohort study. Am J Gastroenterol. 2020;115(6):876–84.
22. Fan JG, Wei L, Zhuang H. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis. 2019;20(4):163–73.

23. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Suppl 1):S81–90.
24. Goodchild M, Zheng R. Tobacco control and healthy China 2030. Tob Control. 2019;28(4):409–13.
25. Callison K, Schiman C, Schiman JC. Smoking cessation and weight gain: evidence from China. Econ Hum Biol. 2021;43:101045.
26. Harris KK, Zopey M, Friedman TC. Metabolic effects of smoking cessation. Nat Rev Endocrinol. 2016;12(5):299–308.
27. Kim K, Park SM, Lee K. Weight gain after smoking cessation does not modify its protective effect on myocardial infarction and stroke: evidence from a cohort study of men. Eur Heart J. 2018;39(17):1523–31.
28. Sahle BW, Chen W, Rawal LB, Renzaho AMN. Weight gain after smoking cessation and risk of major chronic diseases and mortality. JAMA Netw Open. 2021;4(4):e217044.
29. Hawkins J, Hollingworth W, Campbell R. Long-term smoking relapse: a study using the British household panel survey. Nicotine Tob Res. 2010;12(12):1228–35.
30. Li N, Wu P, Wang Z, Shen Y, Zhang L, Xue F, et al. Smoking-related cancer death among men and women in an ageing society (China 2020–2040): a population-based modelling study. Tob Control. 2021. https://doi.org/10.1136/tobaccocontrol-2020-056444.
31. Song SJ, Lai JC, Wong GL, Wong VW, Yip TC. Can we use old NAFLD data under the new MASLD definition? J Hepatol. 2024;80(2):e54–6.

Publisher's Note