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Original Article

Association of Change in Smoking Status and Subsequent Weight Change with Risk of Nonalcoholic Fatty Liver Disease

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Background/Aims: Smoking is considered a risk factor for the development of nonalcoholic fatty liver disease (NAFLD). However, the association of a weight change after a change in smoking status and the risk of NAFLD remains undetermined.

Methods: This study used the Korean National Health Insurance Service-National Sample Cohort. Based on the first (2009 to 2010) and second (2011 to 2012) health examination periods, 139,180 adults aged at least 40 years were divided into nonsmoking, smoking cessation, smoking relapse, and sustained smoking groups. NAFLD was operationally defined using the fatty liver index. The adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated using multivariable-adjusted logistic regression.

Results: Compared to nonsmoking with no body mass index (BMI) change, the risk of NAFLD was significantly increased among subjects with BMI gain and nonsmoking (aOR, 4.07; 95% CI, 3.77 to 4.39), smoking cessation (aOR, 5.52; 95% CI, 4.12 to 7.40), smoking relapse (aOR, 7.51; 95% CI, 4.81 to 11.72), and sustained smoking (aOR, 6.65; 95% CI, 5.33 to 8.29), whereas the risk of NAFLD was reduced among participants with BMI loss in all smoking status groups. In addition, smoking cessation (aOR, 1.76; 95% CI, 1.35 to 2.29) and sustained smoking (aOR, 1.64; 95% CI, 1.39 to 1.94) were associated with higher risk of NAFLD among participants with no BMI change. The liver enzyme levels were higher among participants with smoking cessation and BMI gain.

Conclusions: Monitoring and management of weight change after a change in smoking status may be a promising approach to reducing NAFLD. **(Gut Liver 2023;17:150-158)**

Key Words: Nonalcoholic fatty liver; Screening; Fatty liver index; Smoking cessation; Cohort study

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease with an estimated prevalence of 25% globally.[1] NAFLD has been considered potentially progressive to liver cirrhosis, liver failure, or hepatocellular carcinoma.[2] However, accumulating evidence has suggested its associations with extrahepatic diseases, including metabolic syndrome and cardiovascular disease.[3,4] Considering the increasing prevalence of NAFLD and its extrahepatic complications, it is crucial to determine modifiable risk factors for the development of preventive strategies.

Cigarette smoking is the leading modifiable risk factor for the development of premature morbidity and mortality.[5] It has been found to be a risk factor for the progression of liver diseases, such as alcoholic liver disease and chronic hepatitis virus, and hepatocellular carcinoma.[6] In NAFLD, cigarette smoking was found associated with increased risk of NAFLD.[7,8] However, these studies were limited by evaluating smoking status only without consideration of subsequent weight change. We hypothesized that weight change after change in smoking status could be more definitive in evaluating risk of NAFLD. A better understanding of change in

smoking status and subsequent weight change may provide new insights into NAFLD preventive strategies and support identify individuals at high risk of NAFLD.

Therefore, we evaluated change in smoking status and subsequent weight change in a large-scale cohort study of adult participants who received biennial health screening. We also evaluated whether change in smoking status and subsequent weight change increases liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (γ-GT).

MATERIALS AND METHODS

1. Study population

The National Health Insurance Service (NHIS) of Korea provides obligatory health insurance for all Korean citizens that covers almost all types of healthcare, and the health examination is carried out biennially for all participants aged at least 40 years.[9] The NHIS-National Sample Cohort is a random sampling of the NHIS database with intent to represent Korean citizens, which includes data regarding sociodemographic characteristics, medical history, hospital visit and admission, serologic characteristics, pharmaceutical prescriptions, and lifestyle questionnaires. From 2002 NHIS database, 1,025,340 participants were randomly extracted in the NHIS-National Sample Cohort.

In this study, participants who received health examinations in both two periods (2009–2010 and 2011–2012) were selected for the evaluation on change in smoking status and body mass index (BMI; n=296,033) (Fig. 1). We excluded participants with any type of alcohol consumption in both 2009–2010 and 2011–2012 periods (n=131,145), hepatitis virus infection (n=710; defined using the International Classification of Diseases 10th revision code of B18), and NAFLD in the first health examination (2009–2010; n=13,420). In addition, participants with missing information regarding key variables, including BMI, waist circumference, blood pressure, fasting serum glucose, total cholesterol, triglyceride, ALT, AST, γ-GT, creatinine, moderate-to-vigorous physical activity (MVPA), walking, and smoking status, were excluded. Finally, 139,180 participants with complete information composed the analytic cohort. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: E-2108-136-1246). The requisite for informed consent was waived because the NHIS-National Sample Cohort is anonymized according to the strict confidentiality guidelines.

2. Change in smoking status and weight change

All participants were classified into following four groups: sustained smoker, current smoker in the first health examination (2009–2010) and current smoker in the second health examination (2011–2012), smoking relapser, non-smoker in the first health examination (2009–2010) and current smoker in the second health examination (2011–2012), smoking cessation, current smoker in the first health examination (2009–2010) and non-smoker in the second health examination (2011–2012), and non-smoker, no smoking in both first and second health examinations.

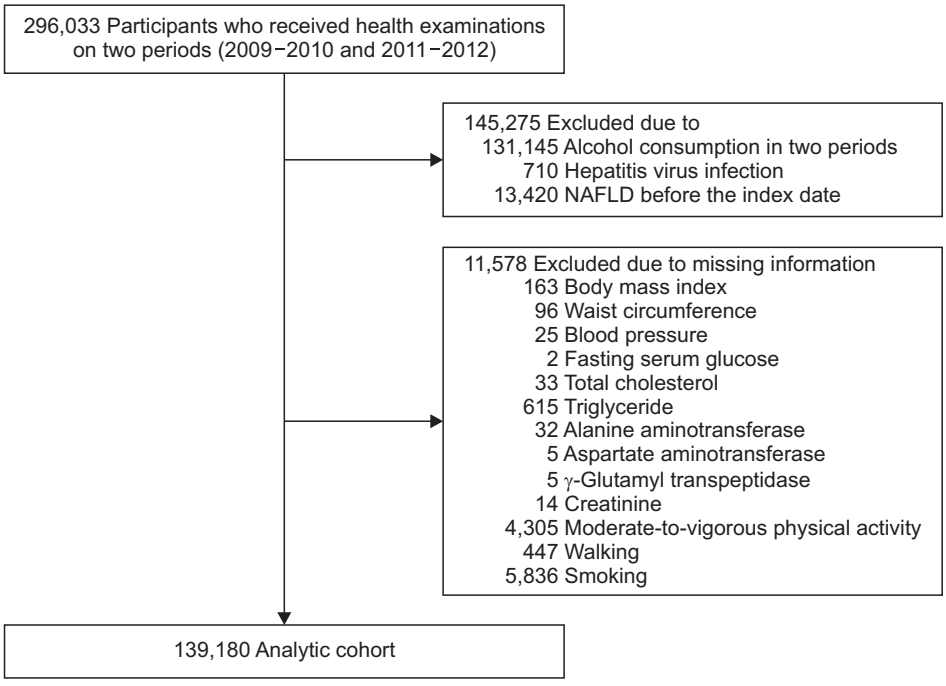

Fig. 1. Flow diagram for inclusion of the study population.
NAFLD, nonalcoholic fatty liver disease.

Change in BMI greater than +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010) was considered as BMI gain. Change in BMI ranging between –1.0 kg/m^2 and +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010) was considered as no BMI change. BMI loss of more than 1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010) was considered as BMI loss.

3. Definition of NAFLD

The presence of NAFLD was operationally defined using the fatty liver index (FLI), which as calculated as follows:[10]

$$FLI=1/(1+\exp[-x])^{-1}\times 100,$$
$$x=0.953\times\log_e(\text{serum triglycerides})+0.139\times(\text{BMI})$$
$$+0.718\times\log_e(\gamma\text{–GT})+0.053\times(\text{waist circumference})-15.745.$$

FLI ≥60 was defined as NAFLD. The FLI is accepted an alternative to imaging studies in a number of practice guidelines.[11] In Korean population, the FLI for diagnosis of NAFLD was validated with an area under curve of 0.87 in receiver operating characteristic curves.[12]

4. Key variables

The following key variables were selected for the adjusted analyses: age (continuous; years), sex (categorical; men and women), household income (categorical; upper half and lower half), BMI (continuous; kg/m^2), hypertension (categorical; yes and no), diabetes mellitus (categorical; yes and no), dyslipidemia (categorical; yes and no), MVPA (categorical; none, 1–4 times/week, and ≥5 times/week), and Charlson comorbidity index (CCI; continuous). In addition, the participants were stratified according to the following variables for subgroup analyses: MVPA (none, 1–4 times/week, and ≥5 times/week), walking (none, 1–4 times/week, and ≥5 times/week), type 2 diabetes mellitus (yes and no), and CCI (0, 1, and ≥2). Hypertension, diabetes mellitus, and dyslipidemia were defined using the ICD-10 codes of I10 with antihypertensive medication use, E10-14 with antidiabetic medication use, and E78 with antidyslipidemic medication use, respectively.

5. Statistical analysis

The primary outcome was NAFLD, which was defined using the FLI in 2011–2012. Continuous and categorical variables were presented as median (interquartile range) and number (%), respectively. Logistic regression model was adopted to estimate odds ratio (OR) and 95% confidence interval (CI) of NAFLD based on the smoking status and subsequent BMI change. The effects of joint categories of the change in smoking status and BMI change were calculated by comparing the category groups with a reference group that is consisted of sustained smokers. We conducted multivariable model after adjustments for age, sex, household income, BMI, hypertension, diabetes mellitus, dyslipidemia, MVPA, and CCI. Adjusted ORs (aOR) are calculated after adjustments for age and sex (model 1), and for all key variables (model 2). Sensitivity analysis was performed using hepatic steatosis index-defined NAFLD (>36), which was calculated as follows: 8×ALT/AST+BMI+2 (if women) +2 (if diabetes mellitus).[13] Secondary analysis was carried out by stratifying participants according to pack-years (0, <10, 10–19.9, and ≥20) to defined the association of weight change in each pack-years group with risk of NAFLD. Household income was evaluated basing on the insurance premium. We used International Classification of Diseases (10th revision) codes to calculate the CCI. Adjusted mean liver enzyme levels were calculated using linear regression analysis after adjustments for age, sex, household income, BMI, hypertension, diabetes mellitus, dyslipidemia, MVPA, and CCI. A p-value of less than 0.05 was considered statistically significant. All data mining and statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the descriptive characteristics of the study participants. There were 39,271 men (28.2%) and 99,909 women (71.8%) with a median age of 57 (interquartile range, 52 to 67 years). The median BMI and waist circumference were 23.5 kg/m^2 and 80 cm, respectively. Non-smoker, smoking cessation, smoking relapser, and sustained smoker groups included 128,569, 2,437, 1,512, and 6,662 participants, respectively. The CCI was 0, 1, and ≥2 in 26,719 (19.2%), 38,268 (27.5%), and 74,193 (53.3%) participants, respectively. The median BMI was 23.5, 23.1, 23.4, and 23.0 kg/m^2 in non-smoker, smoking cessation, smoking relapser, and sustained smoker groups, respectively.

Table 2 depicts the association of change in smoking status and BMI change with NAFLD. Compared with non-smoker with no BMI change, non-smoker with BMI gain (aOR, 4.07; 95% CI, 3.77 to 4.39), smoking cessation with no BMI change (aOR, 1.76; 95% CI, 1.35 to 2.29), smoking cessation with BMI gain (aOR, 5.52; 95% CI, 4.12 to 7.40), smoking relapser with BMI gain (aOR, 7.51; 95% CI, 4.81 to 11.72), sustained smoker with no BMI change (aOR, 1.64; 95% CI, 1.39 to 1.94), and sustained smoker with

Table 1. Baseline Characteristics of the Participants

Characteristic	Overall participant (n=139,180)	Non-smoker (n=128,569)	Smoking cessation (n=2,437)	Smoking relapser (n=1,512)	Sustained smoker (n=6,662)
Age, yr	57 (52–67)	57 (52–67)	59 (52–69)	58 (51–68)	56 (51–66)
Female sex	99,909 (71.8)	98,697 (76.8)	267 (17.7)	396 (16.2)	549 (8.2)
Household income, upper half	86,248 (62.0)	79,832 (62.1)	1,491 (61.2)	922 (61.0)	4,003 (60.1)
Body mass index, kg/m^2	23.5 (21.8–25.3)	23.5 (21.8–25.3)	23.1 (21.3–24.8)	23.4 (21.6–25.1)	23.0 (21.2–24.7)
Waist circumference, cm	80 (74–85)	79 (74–85)	82 (77–87)	82 (78–87)	82 (77–86)
Systolic blood pressure, mm Hg	121 (112–132)	121 (112–132)	120 (110–130)	120 (110–130)	120 (110–130)
Fasting serum glucose, mg/dL	94 (87–103)	94 (87–103)	94 (86–105)	95 (87–105)	94 (86–105)
Total cholesterol, mg/dL	198 (175–224)	199 (175–224)	195 (172–220)	196 (172–219)	196 (173–222)
Triglyceride, mg/dL	108 (78–149)	107 (77–148)	117 (85–162)	121 (87–165)	120 (88–164)
Aspartate aminotransferase, IU/L	23 (19–27)	23 (19–27)	22 (19–27)	23 (19–27)	22 (18–26)
Alanine aminotransferase, IU/L	19 (15–26)	19 (15–26)	20 (16–27)	21 (16–29)	20 (15–28)
γ-Glutamyl transferase, IU/L	19 (14–26)	18 (14–26)	23 (17–32)	24 (18–33)	24 (18–33)
Creatinine, mg/dL	0.8 (0.7–1.0)	0.8 (0.7–1.0)	1.0 (0.8–1.1)	1.0 (0.8–1.1)	1.0 (0.9–1.1)
Moderate-to-vigorous physical activity					
None	76,140 (54.7)	70,461 (54.8)	1,258 (51.6)	922 (61.0)	3,499 (52.5)
1–4 times/wk	56,032 (40.3)	51,611 (40.1)	1,041 (42.7)	536 (35.4)	2,844 (42.7)
≥5 times/wk	7,008 (5.0)	6,497 (5.1)	138 (5.7)	54 (3.6)	319 (4.8)
Walking					
None	48,916 (35.1)	44,904 (34.9)	877 (36.0)	690 (45.6)	2,445 (36.7)
1–4 times/wk	52,351 (37.6)	48,404 (37.6)	910 (37.3)	517 (34.2)	2,520 (37.8)
≥5 times/wk	37,913 (27.2)	35,261 (27.4)	650 (26.7)	305 (20.2)	1,697 (25.5)
Hypertension	51,343 (36.9)	48,332 (37.6)	792 (32.5)	464 (30.7)	1,755 (26.3)
Diabetes mellitus	13,562 (9.7)	12,319 (9.6)	297 (12.2)	179 (11.8)	767 (11.5)
Dyslipidemia	29,337 (21.1)	27,556 (21.4)	415 (17.0)	292 (19.3)	1,074 (16.1)
Charlson comorbidity index					
0	26,719 (19.2)	24,142 (18.8)	552 (22.7)	331 (21.9)	1,694 (25.4)
1	38,268 (27.5)	35,211 (27.4)	708 (29.1)	432 (28.6)	1,917 (28.8)
≥2	74,193 (53.3)	69,216 (53.8)	1,177 (48.3)	749 (49.5)	3,051 (45.8)

Data are presented as median (interquartile range) or number (%).

Table 2. Association of Change in BMI and Smoking Status with Nonalcoholic Fatty Liver Disease

Variable	No. of cases (%)	OR (95% CI)	p-value	aOR (95% CI)*	p-value	aOR (95% CI)†	p-value
Non-smoker							
No BMI change (n=85,929)‡	2,099 (2.4)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
BMI gain (n=20,809)§	1,503 (7.2)	3.11 (2.91–3.33)	<0.001	3.16 (2.95–3.39)	<0.001	4.07 (3.77–4.39)	<0.001
BMI loss (n=21,831)‖	201 (0.9)	0.37 (0.32–0.43)	<0.001	0.37 (0.32–0.43)	<0.001	0.19 (0.16–0.22)	<0.001
Smoking cessation							
No BMI change (n=1,423)‡	69 (4.8)	2.04 (1.59–2.60)	<0.001	1.47 (1.15–1.88)	0.003	1.76 (1.35–2.29)	<0.001
BMI gain (n=682)§	62 (9.1)	3.99 (3.07–5.20)	<0.001	2.85 (2.18–3.73)	<0.001	5.52 (4.12–7.40)	<0.001
BMI loss (n=332)‖	7 (2.1)	0.86 (0.41–1.82)	0.694	0.62 (0.29–1.32)	0.217	0.40 (0.17–0.91)	0.028
Smoking relapser							
No BMI change (n=960)‡	33 (3.4)	1.42 (1.00–2.02)	0.049	1.03 (0.72–1.47)	0.870	1.17 (0.81–1.69)	0.416
BMI gain (n=225)§	28 (12.4)	5.68 (3.81–8.45)	<0.001	4.25 (2.85–6.35)	<0.001	7.51 (4.81–11.72)	<0.001
BMI loss (n=327)‖	1 (0.3)	0.12 (0.02–0.87)	0.036	0.09 (0.01–0.63)	0.015	0.06 (0.01–0.45)	0.006
Sustained smoker							
No BMI change (n=4,527)‡	192 (4.2)	1.77 (1.52–2.06)	<0.001	1.23 (1.05–1.44)	0.009	1.64 (1.39–1.94)	<0.001
BMI gain (n=1,075)§	123 (11.4)	5.16 (4.26–6.26)	<0.001	3.64 (2.99–4.43)	<0.001	6.65 (5.33–8.29)	<0.001
BMI loss (n=1,060)‖	17 (1.6)	0.65 (0.40–1.05)	0.080	0.46 (0.28–0.74)	0.001	0.34 (0.21–0.56)	<0.001

Adjusted odds ratio (aOR) calculated using logistic regression.

BMI, body mass index; OR, odds ratio; CI, confidence interval.

*Adjusted for age and sex; †Adjusted for age, sex, household income, BMI, hypertension, diabetes mellitus, dyslipidemia, moderate-to-vigorous physical activity, and Charlson comorbidity index; ‡With change in BMI ranging between –1.0 kg/m^2 and +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); §With change in BMI greater than +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); ‖With BMI loss of more than 1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010).

BMI gain (aOR, 6.65; 95% CI, 5.33 to 8.29) revealed higher risk of NAFLD, whereas BMI loss was found to be associated with lower risk of NAFLD in all smoking groups.

When stratified participants according to the pack-years, BMI gain showed a significant association with higher risk of NAFLD, whereas BMI loss was associated with lower risk of NAFLD, except for <10 pack-years compared to no BMI change in 0 pack-years group (Supplementary Table 1). In addition, ≥20 pack-years was found significantly unfavorable in participants with no BMI change (aOR, 1.77; 95% CI, 1.50 to 2.09). When defined NAFLD using hepatic steatosis index, the results were generally similar to the FLI-defined NAFLD, except for smoking relapser with no BMI change group that was found to be associated with higher hepatic steatosis index-defined NAFLD but not FLI-defined NAFLD (Supplementary Table 2).

In subgroup analyses, BMI gain and BMI loss were associated with higher and lower NAFLD risk compared to no BMI change among sustained smokers in all stratified subgroups, except for MVPA ≥5 times/week that showed no significant difference (Table 3). Participants with smoking cessation and no BMI change showed not significantly different NAFLD risk compared to sustained smokers with no BMI change. Moreover, smoking cessation and BMI gain had higher NAFLD risk compared to sustained smokers with no BMI change, except for those with MVPA ≥5 times/week and diabetes mellitus that showed no difference. In addition, BMI gain and loss were associated with higher and lower risk of NAFLD compared to no BMI change among non-smokers, respectively (Supplementary Table 3). As for smoking relapsers, most subgroups showed higher risk of NAFLD in BMI gain compared to non-smoker with no BMI change.

Liver enzyme levels also significantly varied among change in smoking status and subsequent BMI change categories (Table 4). Multivariable-adjusted AST was 26.3 IU/L (highest) in non-smoker with BMI gain, followed by smoking cessation with BMI gain, and smoking relapser with BMI gain. Multivariable-adjusted ALT was highest in smoking cessation with BMI gain (28.3 IU/L), followed by smoking relapser with BMI gain, non-smoker with BMI gain, and sustained smoker with BMI gain. As for the multivariable-adjusted γ-GT, the level was highest in smoking cessation with BMI gain (32.4 IU/L), followed by smoking relapser with BMI gain, smoking cessation with BMI loss, and sustained smoker with BMI gain.

DISCUSSION

Based on the nationally representative database that contains health screening data linked to clinical information of more than 150,000 Korean population, we identi-

Table 3. Stratified Analyses of the Association of Change in BMI and Smoking Status with Nonalcoholic Fatty Liver Disease among Sustained Smokers and Quitters

Variable	Sustained smoker			Smoking cessation			p for interaction
	No BMI change*	BMI gain†	BMI loss‡	No BMI change*	BMI gain†	BMI loss‡	
MVPA							0.897
None	1.00 (reference)	4.46 (3.09–6.44)¶	0.14 (0.06–0.34)¶	1.18 (0.77–1.82)	3.88 (2.47–6.11)¶	0.83 (0.36–1.92)	
1–4 times/wk	1.00 (reference)	3.42 (2.31–5.07)¶	0.33 (0.16–0.65)‖	0.93 (0.60–1.45)	2.90 (1.75–4.80)¶	NA	
≥5 times/wk	1.00 (reference)	4.63 (1.32–16.19)§	0.16 (0.02–1.46)	1.68 (0.49–5.73)	2.17 (0.55–8.56)	NA	
Walking							0.442
None	1.00 (reference)	4.87 (3.16–7.51)¶	0.12 (0.04–0.37)¶	1.07 (0.63–1.82)	3.24 (1.86–5.64)¶	0.76 (0.28–2.07)	
1–4 times/wk	1.00 (reference)	2.82 (1.83–4.33)¶	0.33 (0.16–0.68)‖	0.93 (0.58–1.49)	3.47 (2.06–5.85)¶	0.19 (0.04–0.80)§	
≥5 times/wk	1.00 (reference)	5.48 (3.20–9.39)¶	0.22 (0.08–0.64)‖	1.34 (0.74–2.42)	3.65 (1.89–7.05)¶	NA	
Diabetes mellitus							0.546
Yes	1.00 (reference)	3.21 (1.53–6.74)‖	0.20 (0.06–0.67)‖	1.33 (0.65–2.71)	1.27 (0.40–4.00)	NA	
No	1.00 (reference)	4.09 (3.09–5.41)¶	0.23 (0.13–0.40)¶	1.03 (0.74–1.44)	3.65 (2.59–5.13)¶	0.37 (0.16–0.85)§	
CCI							0.363
0	1.00 (reference)	3.22 (1.87–5.57)¶	0.11 (0.03–0.47)‖	1.27 (0.69–2.34)	3.51 (1.86–6.64)¶	NA	
1	1.00 (reference)	4.41 (2.75–7.10)¶	0.14 (0.04–0.50)‖	0.92 (0.52–1.63)	5.06 (2.90–8.82)¶	0.40 (0.10–1.58)	
≥2	1.00 (reference)	4.02 (2.74–5.90)¶	0.31 (0.17–0.59)¶	1.08 (0.71–1.66)	2.23 (1.32–3.76)‖	0.26 (0.09–0.74)§	

Data are adjusted odds ratio (95% confidence interval) after adjustments for age, sex, household income, body mass index (BMI), hypertension, diabetes mellitus, dyslipidemia, moderate-to-vigorous physical activity (MVPA), and Charlson comorbidity index (CCI).
NA, not applicable.
*With change in BMI ranging between −1.0 kg/m^2 and +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); †With change in BMI greater than +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); ‡With BMI loss of more than 1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); §p<0.05; ‖p<0.01; ¶p<0.001.

Table 4. Association of Change in BMI and Smoking Status with Liver Enzyme Levels

Variable	Non-smoker			Smoking cessation			Smoking relapser			Sustained smoker		
	No BMI change*	BMI gain†	BMI loss‡	No BMI change*	BMI gain†	BMI loss‡	No BMI change*	BMI gain†	BMI loss‡	No BMI change*	BMI gain†	BMI loss‡
AST, IU/L												
Median	23.0	23.0	23.0	23.0	24.0	23.0	22.0	22.0	21.0	22.0	22.0	22.0
Unadjusted mean	25.0	25.8	24.8	24.9	26.3	25.1	24.3	25.9	23.4	23.3	24.4	24.5
Model 1§	25.2	26.1	25.0	24.5	25.9	24.7	24.0	25.6	23.0	23.0	24.1	24.1
Model 2‖	25.4	26.3	25.0	24.7	26.2	24.9	24.2	25.9	23.1	23.2	24.3	24.2
ALT, IU/L												
Median	19.0	20.0	28.0	21.0	23.0	19.5	20.0	21.0	19.0	20.0	22.0	18.0
Unadjusted mean	22.3	23.7	21.0	24.5	27.4	24.8	24.5	26.6	21.3	23.3	25.4	23.1
Model 1§	23.2	24.8	22.3	23.3	26.1	24.0	23.1	25.5	20.4	21.4	23.9	21.7
Model 2‖	24.6	26.4	22.9	24.9	28.3	25.0	24.7	27.2	21.3	23.2	26.0	22.9
γ-GT, IU/L												
Median	18.0	19.0	18.0	24.0	26.0	21.0	24.0	26.0	22.0	24.0	26.0	22.0
Unadjusted mean	23.3	25.0	22.6	29.2	33.1	33.0	29.2	32.8	26.6	28.9	31.6	28.6
Model 1§	25.0	26.9	24.5	27.0	30.8	31.0	27.0	31.1	24.6	26.1	29.0	26.1
Model 2‖	26.0	28.0	24.9	28.2	32.4	31.8	28.1	32.2	25.2	27.4	30.4	26.9

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transferase.
*With change in BMI ranging between −1.0 kg/m^2 and +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); †With change in BMI greater than +1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); ‡With BMI loss of more than 1.0 kg/m^2 in the second health examination (2011–2012) compared to the first health examination (2009–2010); §Adjusted mean value after adjustments for age and sex; ‖Adjusted mean value after adjustments for age, sex, household income, BMI, hypertension, diabetes mellitus, dyslipidemia, moderate-to-vigorous physical activity, and Charlson comorbidity index.

fied that BMI change after change in smoking status is strongly associated with risk of NAFLD. Quitter with BMI gain had higher risk of NAFLD, whereas quitter with BMI loss was associated with a reduced risk of NAFLD. The change in FLI was largest and smallest among quitters with BMI gain and quitters with BMI loss, respectively. Although some studies suggested that smoking cessation is important in prevention of NAFLD, our study highlights that weight management after change in smoking status may be more important to reduce the disease burden of NAFLD.

Data from the previous studies show that smoking cessation is accompanied by a substantial weight gain. Japanese men aged between 19 and 69 years who successfully quit smoking had gained 2.0 kg of weight within 6 months after smoking cessation.[14] In addition, Korean men aged over 30 with a mean smoking cessation interval time of 1.7 years had gained a median weight of 1.3 kg.[15] These weight gain after smoking cessation was considered acceptable since it showed no association with an increased risk of cardiovascular disease or chronic diseases.[16,17] Jung *et al.*[7] previously have found that current smoking and pack-years are associated with higher risk of incident NAFLD among young and middle-aged men and women after adjustments for time-varying variables, including BMI. However, there remained a study determining the combined association of weight change and change in smoking status with risk of NAFLD. Our data show that weight management after change in smoking status is strongly associated with an increased risk of NAFLD. Considering the average weight and height of Koreans aged over 40 years, BMI gain of more than 1.0 kg/m^2 can be translated into an approximate weight gain of more than 2.0 kg.[18] Therefore, our data may be interpreted as more than 2.0 kg of weight gain should be avoided or BMI loss needs to be encouraged after change in smoking status in order to prevent NAFLD.

Currently, only a few studies have evaluated the effects of smoking on NAFLD events, and none of them taken subsequent weight change into account. A retrospective cohort study of 199,468 adults without NAFLD at baseline showed that current smoking is associated with the risk of incident NAFLD.[7] Another study of 13,466 men and women who received abdominal ultrasonography demonstrated that smoking history and current smoking are strongly associated with the severity and prevalence of NAFLD.[19] In addition, a meta-analysis has concluded that smoking, including passive smoking, is significantly associated with NAFLD.[20] Regarding the association of smoking status with the risk of NAFLD, our study further suggested that smoking cessation of 2 years is insufficient to have its beneficial effect against the development of NAFLD. Therefore, participants within 2 years after smoking cessation are still at high risk for NAFLD, thus requires more intensive monitoring for NAFLD compared to general population.

Although we found no significant difference in NAFLD risk between sustained smoking and smoking cessation within 2 years after change in smoking status, smoking cessation is suggested to reverse cigarette smoking-related negative health effects. Cigarette smoking is considered to accelerate heart rate and elevate blood pressure in short-term, which may lead to atherosclerosis if continued over time.[21,22] In addition, smoking is suggested to contribute to increased inflammatory marker levels, which may be improved after smoking cessation.[23] A previous study also found that smoking cessation is associated with attenuative changes in C-reactive protein, albumin, white blood cells, and serum fibrinogen in both temporal and dose-dependent terms.[24] Although smoking cessation may not immediately provide beneficial effects on NAFLD risk and still suffer from the residual effects of cigarette smoking, long-term smoking cessation may improve insulin sensitivity, which may lead to improvement in overall health status and prevention of NAFLD.[22,25]

A previous study reported that glutathione S-transferase genotypes, which protect cells against oxidative stress and have association with the development of cardiovascular disease and diabetes mellitus, are interactively associated with the risk of NAFLD.[26] In addition, the polymorphisms of resistin and glutathione peroxidase-1 genes are suggested to be closely correlated with cigarette smoking and the pathogenesis of NAFLD.[27,28] Since smoking cessation may reverse negative health effect on NAFLD from smoking, changes in underlying biological mechanisms after change in smoking status and subsequent weight change may be noteworthy to develop new therapeutic strategies for NAFLD, which awaits future studies to identify.

Strengths of this study come from adopting a large population with reliable health examination and claims records to evaluate the association of change in smoking status and subsequent BMI change with the risk of NAFLD. BMI in the NHIS health examination was measured by trained professionals, which may be more accurate than self-reported survey on weight. We could also take various potential risk factors for the development of NAFLD, such as CCI and diabetes mellitus. Despite above strengths, some limitations of the present study should be considered. First, smoking status information was collected by a self-reported questionnaire without laboratory examinations. Information regarding the intensity of nicotine addiction were not available. However, there is a number of well-regarded population-based cohort studies that used self-reported questionnaire in assessing smoking status.[29] In addition, we were only able to defined NAFLD using the FLI and hepatic steatosis index due to data unavailability. Therefore, liver biopsy or imaging modalities-based validation is necessary before direct interpretation of our results. Since the FLI calculation involves BMI, our results may seem to be an inevitable result, but the FLI is considered one variable representing the NAFLD status. By using the FLI, we could evaluate the change in fatty liver status after change in smoking status and weight change. In addition, exclusion of participants with alcohol consumption was based on a questionnaire consisted of questions that ask frequency of alcohol consumption (day/week) and amount of alcohol consumption at one time. The amount of alcohol consumption is collected basing on those who answered to drink at least once a week. Therefore, the study population may have included participants who drink less than once a week. Furthermore, we were unable to know the reason for smoking cessation. It is possible that the quitters may have experienced a certain disease due to smoking, which may have affected the results to a certain degree, and it was the major reason for the inclusion of CCI as an adjustment variable in multivariable analyses.

In this large-scale cohort study of middle-aged Korean adults, BMI gain after smoking cessation significantly altered the potential protective association of smoking cessation with the risk of NAFLD after fully adjusting for sociodemographic and serologic characteristics, lifestyle behaviors, CCI, and baseline FLI. Clinicians should recommend weight management after change in smoking status to reduce the disease burden of NAFLD despite the concerns raised regarding the negative association of weight gain after smoking cessation with other diseases. Based on our data, we conclude that weight gain after change in smoking status is a serious health concern for NAFLD in middle-aged Korean adults. Future studies of the multi-ethnic cohorts are required to testify the generalizability of our findings.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: S.J., Y.H.O., S.C., S.M.P. Data acquisition: S.J., S.C., J.C., S.M.K., S.J.P., S.M.P. Data analysis and interpretation: S.J., S.C., J.C., S.M.K., S.J.P. Drafting of the manuscript: S.J., Y.H.O., S.C., S.M.P. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: S.J., S.C., J.C., S.M.K., S.J.P. Obtained funding: S.M.P. Administrative, technical, or material support: S.C., J.C., S.M.K., S.J.P. Study supervision: S.M.P. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. Gastroenterology 2020;158:1851-1864.
2. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330-344.
3. Jeong S, Kim K, Chang J, et al. Development of a simple nonalcoholic fatty liver disease scoring system indicative of metabolic risks and insulin resistance. Ann Transl Med 2020;8:1414.
4. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. Clin Gastroenterol Hepatol 2021;19:2138-2147.
5. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224-2260.
6. Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst 2004;96:1851-1856.
7. Jung HS, Chang Y, Kwon MJ, et al. Smoking and the risk of non-alcoholic fatty liver disease: a cohort study. Am J Gastroenterol 2019;114:453-463.
8. Hamabe A, Uto H, Imamura Y, et al. Impact of cigarette smoking on onset of nonalcoholic fatty liver disease over a 10-year period. J Gastroenterol 2011;46:769-778.
9. Seong SC, Kim YY, Khang YH, et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017;46:799-800.
10. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
11. 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;64:1388-1402.
12. Lee YH, Bang H, Park YM, et al. Non-laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: development, validation and comparison with other scores. PLoS One 2014;9:e107584.
13. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503-508.
14. Tamura U, Tanaka T, Okamura T, et al. Changes in weight, cardiovascular risk factors and estimated risk of coronary heart disease following smoking cessation in Japanese male workers: HIPOP-OHP study. J Atheroscler Thromb 2010;17:12-20.
15. Yoon C, Goh E, Park SM, Cho B. Effects of smoking cessation and weight gain on cardiovascular disease risk factors in Asian male population. Atherosclerosis 2010;208:275-279.
16. 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;39:1523-1531.
17. Sahle BW, Chen W, Rawal LB, Renzaho AM. Weight gain after smoking cessation and risk of major chronic diseases and mortality. JAMA Netw Open 2021;4:e217044.
18. Hong S, Oh HJ, Choi H, et al. Characteristics of body fat, body fat percentage and other body composition for Koreans from KNHANES IV. J Korean Med Sci 2011;26:1599-1605.
19. Takenaka H, Fujita T, Masuda A, Yano Y, Watanabe A, Ko-

dama 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:E102-E112.
20. Akhavan Rezayat A, Dadgar Moghadam M, Ghasemi Nour M, et al. Association between smoking and non-alcoholic fatty liver disease: a systematic review and meta-analysis. SAGE Open Med 2018;6:2050312117745223.
21. Siasos G, Tsigkou V, Kokkou E, et al. Smoking and atherosclerosis: mechanisms of disease and new therapeutic approaches. Curr Med Chem 2014;21:3936-3948.
22. Primatesta P, Falaschetti E, Gupta S, Marmot MG, Poulter NR. Association between smoking and blood pressure: evidence from the health survey for England. Hypertension 2001;37:187-193.
23. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J 2005;26:1765-1773.
24. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med 2005;2:e160.
25. Eliasson B, Attvall S, Taskinen MR, Smith U. Smoking cessation improves insulin sensitivity in healthy middle-aged men. Eur J Clin Invest 1997;27:450-456.
26. Oniki K, Hori M, Saruwatari J, et al. Interactive effects of smoking and glutathione S-transferase polymorphisms on the development of non-alcoholic fatty liver disease. Toxicol Lett 2013;220:143-149.
27. Boyraz M, Cekmez F, Karaoglu A, Cinaz P, Durak M, Bideci A. Serum adiponectin, leptin, resistin and RBP4 levels in obese and metabolic syndrome children with nonalcoholic fatty liver disease. Biomark Med 2013;7:737-745.
28. Samy W, Hassanian MA. Paraoxonase-1 activity, malondialdehyde and glutathione peroxidase in non-alcoholic fatty liver disease and the effect of atorvastatin. Arab J Gastroenterol 2011;12:80-85.
29. Carter BD, Abnet CC, Feskanich D, et al. Smoking and mortality: beyond established causes. N Engl J Med 2015;372:631-640.