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Research Letter

Associations Between Active, Passive Smoking and the Risk of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease with an estimated worldwide prevalence of 32.4%.[1] The multisystem condition is related to an increased risk of liver-related and cardiovascular extrahepatic diseases.[2] Smoking is the leading preventable risk factor for premature disability and mortality. As NAFLD and smoking are both associated with the development of metabolic features, there has been increasing interest in testing the relationship between smoking and NAFLD. The causal relevance of smoking to NAFLD incidence have been implicated in cross-sectional and prospective cohort studies.[3,4] However, previous studies mainly focused on the effect of active smoking, discussion on the influence of passive smoking on NAFLD will facilitate illustrating the association between smoking and NAFLD. We conducted a national two-center cross-section study of active, passive smoking and NAFLD risk in Chinese and European population. This design allowed us to (1) test for associations between active, passive smoking and NAFLD risk by sex and consolidate evidence for causality by estimating dose-response relationship, (2) identify mediated factors, and (3) resolve their possible interaction with smoking.

In this study, we reported results from the UK Biobank study (application number: 85248), a large-scale, prospective study which recruited more than 500,000 participants from 40 to 70 years of age,[5] and independently validated the association in a Chinese population, the Nanjing Health Examination Cohort (NJHE Cohort). All participants provided written informed consent. The UK Biobank obtained ethical approval from the NHS National Research Ethics Service. After excluded those with missing data on NAFLD diagnosis and smoking status, high alcohol consumption or baseline liver diseases (Supplementary Table 1), 14,348 and 11,211 participants were included in further analysis, respectively (Supplementary Fig. 1). Smoking status was classified as non-, current, former, and passive smokers. NAFLD diagnosis was based on the presence of three findings, (1) evidence of hepatic steatosis by either histology or imaging, (2) without heavy alcohol consumption, (3) without history of specific diseases that could lead to steatosis.

Log-binomial logistic regression was used to examine the association of active, passive smoking with NAFLD risk by sex, in which age, ethnicity, education level, physical activity, and drinking status were adjusted. To assess the influence of potential mediating factors, we further adjusted for body mass index (BMI), triglycerides, fasting blood glucose, high-density lipoprotein cholesterol (HDL-C) and waist-hip ratio (UK Biobank only) and performed mediation analysis using the above variables as potential mediators. Stratified analyses were conducted to assess interaction effects of aforementioned variants. Generalized additive models (GAMs) were used to evaluate nonlinear relations between exposure to secondhand smoke and the value of liver proton density fat fraction (PDFF) among nonsmokers in UK Biobank. Mendelian randomization (MR) analyses between smoking initiation and NAFLD were performed to consolidate the association. We then calculated category-specific population attributable fraction (PAF), a fraction of total NAFLD risk in the population that would be eliminated if persons in the specific exposure category shifted to the low-risk group.[6] We performed a series of sensitivity analyses to test the stability of the results. First, we restricted

Abbreviations: BMI, body mass index; CI, confidence interval; GAM, generalized additive model; HDL-C, high-density lipoprotein cholesterol; IVW, inverse-variance weighted; LDL-C, low-density lipoprotein cholesterol; MR, mendelian randomization; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NJHE Cohort, Nanjing Health Examination Cohort; OR, odds ratio; PAF, population attributable fraction; PDFF, proton density fat fraction.

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the analysis to participants with complete covariates. Second, in order to consist with the definition in UK Biobank, we redefined passive smoker in the NJHE Cohort. Third, we restricted the analysis to those 40 years of age or older in the NJHE Cohort to coincide with the age distribution in UK Biobank. Fourth, we adopted a more rigorous exclusion criteria to ensure the specificity of smoking with NAFLD. Detailed information on methods and statistical analyses are provided in the Supplementary File 1.

The baseline characteristics of study participants from the UK Biobank and NJHE Cohort are shown in Table 1. We observed a higher prevalence of NAFLD in Chinese men (40.03%), but a lower rate in Chinese women (13.40%). Compared with nonsmokers, current smokers had a significantly higher NAFLD risk in both sexes in the UK Biobank (adjusted OR, 1.39 [1.06–1.81] and 1.75 [1.37–2.24] for men and women, respectively; Fig. 1). An equivalent effect for men was observed in the NJHE Cohort, with an adjusted OR of 1.36 [1.19–1.57]. Female passive smoking in women was found prominently associated with an increased risk of NAFLD (adjusted OR, 1.60 [1.37–1.89] and 1.26 [1.07–1.48] in the UK Biobank and NJHE Cohort, respectively), not in men. Strength of the aforementioned association was weakened after adjusted for potential mediators. The results were substantially unchanged in sensitivity analyses (Supplementary Tables 2–5). What is more, greater cumulative cigarettes consumptions, shorter durations of smoking cessation and longer duration of secondhand smoke exposure showed stronger associations with NAFLD risk (Supplementary Table 6). The dose-response relationship was also found through the GAM (Supplementary Fig. 2), where substantially rising curves were observed when we assessed the association between absolute exposure of secondhand smoke and value of liver PDFF among female nonsmokers in the UK Biobank (p=0.001 for exposure at home and p<0.001 for exposure outside home). Ensured the absence of pleiotropy (MR Egger's intercept p-value=0.086) and homogeneity (the p-value for heterogeneity was 0.218) of instrumental variables, we used the results from inverse-variance weighted (IVW) in MR analysis (Supplementary Table 7), and found that genetic liability to smoking initiation was positively associated with NAFLD (OR, 1.76 [1.29–2.41]; $p=3.65\times10^{-4}$).

In stratified analysis (Supplementary Figs. 3–4), the associations between smoking status and NAFLD risk were stronger among those with abnormal metabolic condition. On this basis, we found that the percentages of the effect mediated by BMI, triglycerides, HDL-C, and waist-hip ratio were estimated as 25.00%, 10.71%, 2.38% and 14.29% in the association between female passive smoking and NAFLD risk in the UK Biobank (Fig. 2), and the relations between active smoking and NAFLD risks were significantly mediated by aforementioned factors in both sexes (Supplementary Fig. 5). PAFs for population counterfactuals were reported in Supplementary Table 8. In the UK Biobank, if passive smokers avoided exposure to secondhand smoke, 5.70% [3.40–7.95%] of observed NAFLD cases could have been averted in the whole population, while an absolute higher PAF (8.25% [5.19–11.22%]) was calculated for women. More detailed description of results is provided in Supplementary File 2.

In our study, patterns of association between smoking status and NAFLD varied among the multi-ethnic populations. Both male and female active smokers were related to increased risk of NAFLD in the UK Biobank, while the positive association was only observed among men in the NJHE Cohort. Similarly, a cross-sectional analysis also reported a positive association between current smoking and NAFLD risk among Korean men but not among women.[7] Low exposure rate of smoking in Asian women may account for the sex heterogeneity.[8] Additionally, dose-response relationship results further reinforced the causality correlation. In the present study, accumulated pack-year was strongly associated with the severity of NAFLD. Among former smokers who have quit smoking for more than 15 years, the association with the risk of NAFLD was weakened. This variation trend might be regulated by a greater decrease in insulin resistance, which was verified in a Korean study.[9] Previous studies on a potential association between passive smoking and the NAFLD risk have shown conflicting results. A Finnish longitudinal cohort revealed that passive smoking in both child and adult lives were associated with increased risk of adult fatty liver.[3] Data from the National Health and Nutrition Examination Survey failed finding the positive association between NAFLD and serum cotinine level.[10] Our study demonstrated that a longer duration of secondhand smoke exposure was significantly associated with the risk of NAFLD in both sexes.

Smoking is proved to be associated with an increase in low-density lipoprotein cholesterol (LDL-C), plasma triglycerides, and insulin resistance as well as a decrease in plasma HDL-C levels,[11,12] which are also relevant to the occurrence of NAFLD.[13] Emerging evidence now suggests that nicotine in the blood exacerbates hepatic steatosis through increased oxidative stress, hepatocellular apoptosis, and decreased phosphorylation (inactivation) of adenosine-5-monophosphate-activated protein kinase, leading to increased hepatic lipogenesis.[14] Given these findings, we explored the potential pathways and affirmed that the associations of smoking with NAFLD were mediated through above factors, consistent with previous findings that cigarette smoking is a cofactor of lipid profiles in hepatic steatosis,[15] highlighting the necessity of smoking cessation, especially among those of abnormal metabolic markers who were more vulnerable to fatty liver. To the best of our knowledge, this is the first study to reveal the public health implications of cigarette control on the incidence of NAFLD using the calculation of PAFs. Among women about 7% of NAFLD cases could be attributed to secondhand smoke exposure, suggesting that effective strategies should be implemented on preventing secondhand smoke exposure.

The present study has several limitations. The cross-sectional study limited our ability to establish a temporal relationship between smoking and NAFLD, and internal exposure such as serum cotinine level requires evidence of the association of smoking exposure and NAFLD. In summary, our study extends the range of adverse health outcomes positively associated with cigarette exposure, lending robust support to smoking intervention on the reduction of NAFLD in multi-ethnic populations.

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Table 1. Baseline characteristics of participants according to NAFLD by sex[†]

Characteristic	UK Biobank, *n*=14,348					
	Men			Women		
	NAFLD, *n*=1,738	No NAFLD, *n*=4,332	*p*-value	NAFLD, *n*=1,595	No NAFLD, *n*=6,683	*p*-value
Age, year	55.05 (7.42)	55.25 (7.80)	0.363	54.41 (7.03)	53.66 (7.36)	<0.001
Ethnicity						
White ethnicity/Han nationality	1,685 (96.95)	4,200 (96.95)	0.657	1,551 (97.24)	6,536 (97.80)	0.220
Other	50 (2.88)	119 (2.75)		42 (2.63)	133 (1.99)	
Unknown	3 (0.17)	13 (0.30)		2 (0.13)	14 (0.21)	
Education level						
College or University degree	702 (40.39)	2,192 (50.60)	<0.001	576 (36.11)	3,083 (46.13)	<0.001
Other level	875 (50.35)	1,810 (41.78)		836 (52.41)	3,109 (46.52)	
Unknown	161 (9.26)	330 (7.62)		183 (11.47)	491 (7.35)	
Body mass index, kg/m^2	29.16 (4.10)	26.19 (3.34)	<0.001	29.56 (5.09)	25.25 (4.04)	<0.001
Physical activity						
Yes	744 (42.81)	2,181 (50.35)	<0.001	600 (37.62)	2,965 (44.37)	<0.001
No	773 (44.48)	1,632 (37.67)		706 (44.26)	2,554 (38.22)	
Unknown	221 (12.72)	519 (11.98)		289 (18.12)	1,164 (17.42)	
Drinking status						
Never	44 (2.53)	104 (2.40)	0.985	64 (4.01)	191 (2.86)	0.107
Former	47 (2.70)	114 (2.63)		33 (2.07)	149 (2.23)	
Current	1,646 (94.71)	4,112 (94.92)		1,498 (93.92)	6,342 (94.90)	
Unknown	1 (0.06)	2 (0.05)		0	1 (0.01)	
Smoking status						
Nonsmoker	914 (52.59)	2,628 (60.66)	<0.001	900 (56.43)	4,413 (66.03)	<0.001
Passive smoker	258 (14.84)	626 (14.45)		252 (15.80)	755 (11.30)	
Former smoker	472 (27.16)	902 (20.82)		346 (21.69)	1,258 (18.82)	
Current smoker	94 (5.41)	176 (4.06)		97 (6.08)	257 (3.85)	
Pack years of smoking	24.32 (18.70)	19.37 (15.80)	<0.001	20.26 (15.54)	15.66 (12.14)	<0.001
Duration of smoking cessation, year	18.51 (11.49)	22.04 (11.57)	<0.001	17.62 (11.26)	19.41 (11.12)	0.005
Exposure of SHS at home, hour per week[‡]	0.50 (4.16)	0.21 (2.59)	0.007	0.41 (3.56)	0.27 (2.88)	0.168
Exposure of SHS outside home, hour per week[§]	0.48 (2.58)	0.32 (1.62)	0.013	0.38 (1.89)	0.21 (0.86)	<0.001
Fasting blood glucose, mmol/L	5.16 (1.17)	4.95 (0.83)	<0.001	5.07 (1.05)	4.91 (0.71)	<0.001
Triglycerides, mmol/L	2.27 (1.17)	1.76 (0.91)	<0.001	1.84 (0.92)	1.31 (0.65)	<0.001
HDL-C, mmol/L	1.19 (0.24)	1.31 (0.27)	<0.001	1.48 (0.31)	1.66 (0.34)	<0.001
Waist-hip Ratio	0.95 (0.06)	0.91 (0.06)	<0.001	0.85 (0.06)	0.79 (0.06)	<0.001

(continued)

Table 1. *(continued)*

Characteristic	NJHE Cohort, *n*=11,211					
	Men			Women		
	NAFLD, *n*=2,029	No NAFLD, *n*=3,040	*p*-value	NAFLD, *n*=823	No NAFLD, *n*=5,319	*p*-value
Age, year	39.09 (10.91)	36.55 (10.79)	<0.001	44.89 (11.84)	37.46 (9.40)	<0.001
Ethnicity						
White ethnicity/Han nationality	1,984 (97.78)	2,982 (98.09)	0.443	811 (98.54)	5,226 (98.25)	0.550
Other	45 (2.22)	58 (1.91)		12 (1.46)	93 (1.75)	
Unknown	0	0		0	0	
Education level						
College or University degree	1,899 (93.59)	2,907 (95.63)	0.001	712 (86.51)	5,023 (94.44)	<0.001
Other level	130 (6.41)	133 (4.38)		110 (13.37)	295 (5.55)	
Unknown	0	0		1 (0.12)	1 (0.02)	
Body mass index, kg/m^2	26.71 (3.02)	23.44 (2.50)	<0.001	25.62 (3.33)	21.49 (2.33)	<0.001
Physical activity						
Yes	416 (20.50)	489 (16.09)	<0.001	242 (29.40)	1,559 (29.31)	0.393
No	1,613 (79.50)	2,547 (83.78)		577 (70.11)	3,748 (70.46)	
Unknown	0	4 (0.13)		4 (0.49)	12 (0.23)	
Drinking status						
Never	1,520 (74.91)	2,312 (76.05)	0.488	791 (96.11)	5,155 (96.92)	0.003
Former	9 (0.44)	11 (0.36)		0	1 (0.02)	
Current	499 (24.59)	717 (23.59)		30 (3.65)	163 (3.06)	
Unknown	1 (0.05)	0		2 (0.24)	0	
Smoking status						
Nonsmoker	1,003 (49.43)	1,742 (57.30)	<0.001	502 (61.00)	3,491 (65.63)	0.051
Passive smoker	290 (14.29)	450 (14.80)		315 (38.27)	1,785 (33.56)	
Former smoker	160 (7.89)	165 (5.43)		1 (0.12)	15 (0.28)	
Current smoker	576 (28.39)	683 (22.47)		5 (0.61)	28 (0.53)	
Pack years of smoking	12.11(12.97)	10.24(12.79)	0.004	5.95(6.78)	2.40(3.31)	0.042
Duration of smoking cessation, year	6.91(8.30)	5.96(7.24)	0.366	1.13(1.24)	4.58(3.62)	0.012
Exposure of SHS at home, hour per week‡	19.07 (13.06)	16.01 (12.38)	0.007	21.17 (11.03)	16.72 (10.13)	<0.001
Exposure of SHS outside home, hour per week§	2.01 (2.65)	1.86 (2.58)	0.216	1.58 (2.54)	1.58 (2.39)	0.999
Fasting blood glucose, mmol/L	5.34 (1.18)	4.99 (0.65)	<0.001	5.47 (1.35)	4.87 (0.50)	<0.001
Triglycerides, mmol/L	2.18 (1.53)	1.33 (0.82)	<0.001	1.84 (1.10)	1.01 (0.49)	<0.001
HDL-C, mmol/L	1.14 (0.20)	1.29 (0.25)	<0.001	1.29 (0.25)	1.54 (0.29)	<0.001
Waist-hip Ratio	–	–	–	–	–	–

†*p*-values were calculated using Student's *t*-test for equal variances, Kruskal-Wallis test for unequal variances and χ^2 tests for categorical variables. Values are mean (SD) or *n* (%). ‡The unit of this variable in NJHE Cohort is year. §The unit of this variable in NJHE Cohort is hour per day. HDL-C, high-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; SHS, secondhand smoke.

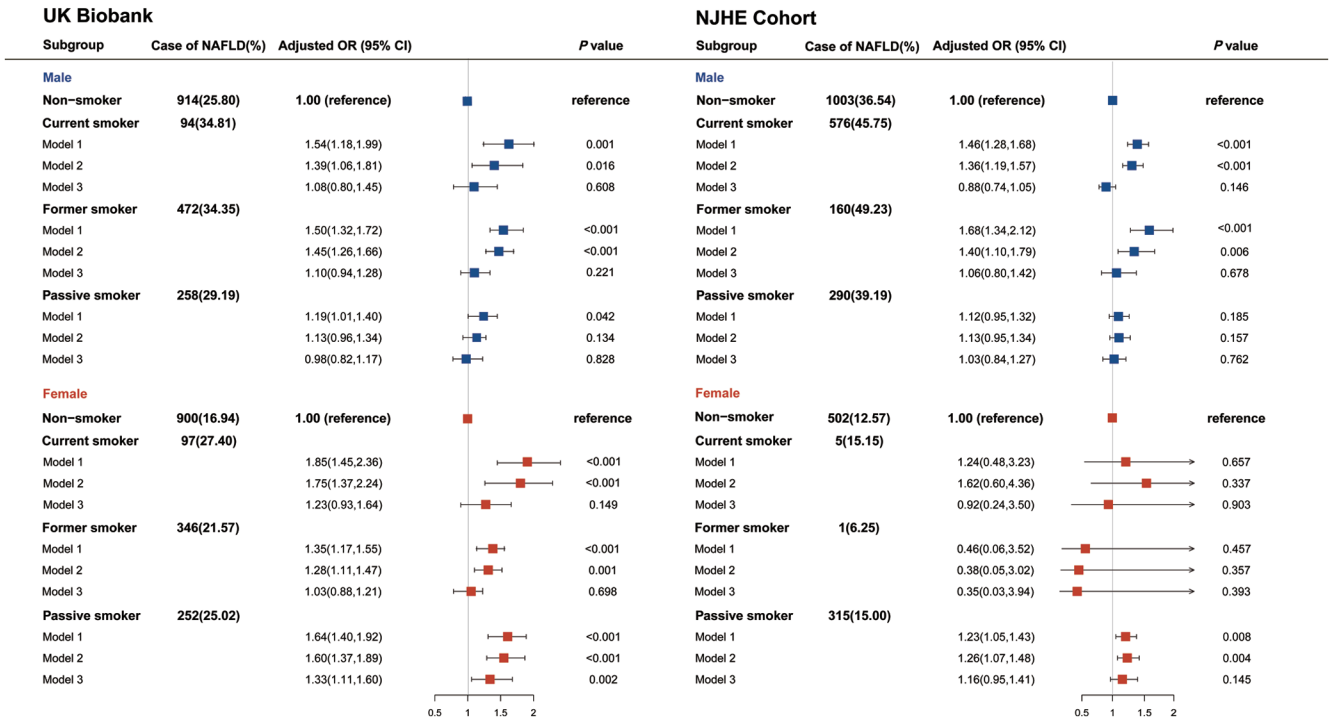

Fig. 1. Association between risk of NAFLD and smoking status by sex. Odds ratios (ORs) were derived from logistic regression models. Model 1: unadjusted. Model 2: adjusted for age, ethnicity, physical activity, education level, drinking status. Model 3: model2+BMI, triglycerides, fasting blood glucose, HDL-C, waist-hip ratio (UK Biobank only). BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

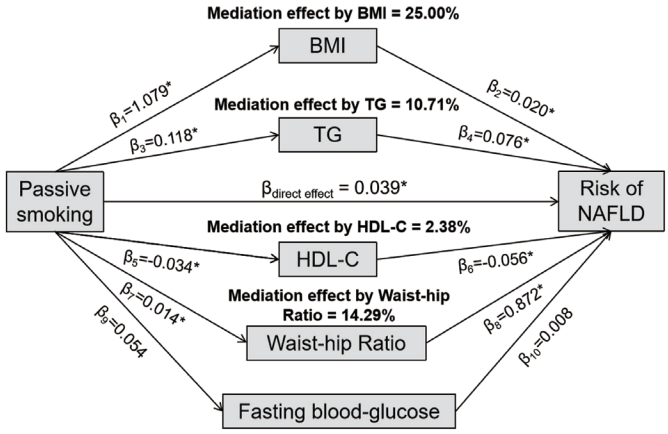

Fig. 2. Mediation effects of BMI, TG, HDL-C, FBG and WHR on the association between female passive smoking and risk of nonalcoholic fatty liver disease in UK Biobank. Data are regression coefficients adjusted for age, ethnicity, physical activity, education level, and drinking status; *p<0.05 for coefficients different from 0. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TG, triglycerides.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceived the study design and supervised the entire project (HS, CS), data interpretation, data analysis, and writing of the draft (XG, CS), and study design and data interpretation in this analysis (XG, CY, JL). All authors reviewed or revised the draft, and approved the submitted draft.

Ethical statement

UK Biobank has full ethical approval from the NHS National Research Ethics Service (21/NW/0157).

Data sharing statement

The Nanjing Health Examination Cohort data used to support

the findings of this study have not been made available; The UK Biobank data are available from https://www.ukbiobank.ac.uk/. Restrictions apply to the availability of these data, which were used under license for the current study (Project ID: 85248). Data are available for bona fide researchers upon application to the UK Biobank.

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