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Article

Smoking and Risk of Fatty Liver Disease: A Meta-Analysis of Cohort Studies

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Abstract: It remains inconclusive whether smoking is associated with an increased risk of fatty liver disease (FLD). We investigated the association between smoking and the risk of FLD by using a meta-analysis of cohort studies. PubMed and EMBASE were searched using keywords from inception to September 2023 to identify relevant studies. Out of 806 articles searched from databases, a total of 20 cohort studies were included in the final analysis. In the meta-analysis, smoking was significantly associated with an increased risk of FLD (odds ratio/relative risk/hazard ratio, 1.14; 95% confidence interval, 1.05 – 1.24; n = 20). Subgroup analyses showed a significant positive association between them in prospective cohort studies (odds ratio/relative risk/hazard ratio, 1.15; 95% confidence interval, 1.05 – 1.18; n = 5), but not in retrospective cohort studies and cross-sectional studies based on cohort studies. In the subgroup meta-analysis by gender in Asians, smoking significantly increased the risk of FLD in men, while there was no significant association between them in women. This meta-analysis showed that smoking increases the risk of FLD. In addition to well-known risk factors of FLD such as obesity and alcohol consumption, clinicians should recommend smoking cessation for the management of FLD.

Keywords: smoking; fatty liver disease; cohort study; meta-analysis

1. Introduction

Fatty liver disease (FLD), which is categorized into two major types such as nonalcoholic FLD (NAFLD) or alcoholic FLD (AFLD), indicates a morphological spectrum consisting of hepatic steatosis and steatohepatitis [1]. It is a persistent liver condition marked by macrovesicular steatosis in liver cells, which has the potential to advance to hepatic cirrhosis, liver failure, and possibly hepatocellular carcinoma [1]. Ethanol consumption serves as a pivotal determinant in distinguishing between NAFLD and AFLD in the guidelines from the European Association for the Study of the Liver [2]. NAFLD diagnosis involves considering ethanol intake of 20 g/d or less in females and 30 g/d or less in males, following the thorough exclusion of alternative causes such as hepatitis virus infection and the use of steatogenic drugs [3]. Beyond alcohol-related impacts, the pathogenesis of FLD is intricately linked to various contributors, including insulin resistance (IR), oxidative stress, mitochondrial dysfunction, immune system deregulation, and the release of adipokines [3,4]. These factors collectively underscore the complexity of FLD, emphasizing the importance of a

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comprehensive understanding to address its progression and associated risks such as hepatic cirrhosis, liver failure, and hepatocellular carcinoma [5].

The overall prevalence of NAFLD worldwide also has increased from 25.5% in or before 2005 to 37.8% in 2016 or later based on the report from a recent meta-analysis published in 2022 [6]. Also, FLD has become a predominant chronic liver disorder in developed Western countries [7]. Its risk factors include a higher body mass index (BMI), consumption of saturated fat and fructose, type 2 diabetes, and known single nucleotide polymorphisms [8].

However, it remains unclear whether smoking is associated with an increased risk of FLD. An animal study has reported that smoking increases lipid accumulation in hepatocytes by modulating an activity of critical molecules related with lipid synthesis [9]. Also, another animal study has shown that the histological severity of NAFLD in obese rats was exacerbated by tobacco exposure [10].

In the meantime, observational epidemiological studies [11–30] have reported inconsistent findings. Several cohort studies [14,17,18,20,23,24,27–29] have reported that smoking was associated with an increased risk of FLD, whereas other cohort studies [11–13,15,16,19,22,26] have reported no significant association between them.

In 2018, the only meta-analysis of observational studies has reported that smoking was significantly associated with the increased risk of NAFLD [31]. However, it included a small number of cohort studies to confirm the association, and subsequent cohort studies have been published since then. Furthermore, to our knowledge, no meta-analysis of cohort studies has been published regarding the association between smoking and the risk of FLD encompassing NAFLD and AFLD.

This study aimed to explore the associations between smoking and the risk of FLD by using a comprehensive meta-analysis of cohort studies and subgroup meta-analyses by important factors.

2. Materials and Methods

2.1. Search Strategy

PubMed and EMBASE were searched in September 2023 with terms of the National Library of Medicine (NLM) Medical Subject Headings (MeSH) and commonly used keywords. We used a PICO framework to combine search terms: P for population is any type of population; I for intervention is ‘smoking; C for comparison is ‘non-smoker’; and O for outcome is ‘fatty liver disease’. Also, the study type was confined to cohort studies. Thus, the final search terms were ‘smoking’, ‘fatty liver disease’, and ‘cohort study’.

2.2. Study Selection and Data Extraction

We included a cohort study that explored the associations between smoking and FLD (NAFLD or AFLD) and presented risk estimates such as odds ratio (OR), relative risk (RR), or hazard ratio (HR) with their corresponding 95% confidence intervals (CI). Two independent authors (MH. Lee and SH. Lee) conducted a selection of relevant studies by reviewing titles and abstracts. Discrepancies between them were resolved through discussion. The extracted information included the last name of the first author, publication year, study region, study design (prospective or retrospective cohort study), gender, study participants, comparison of exposure, risk estimates (OR, RR, and HR with corresponding 95% CIs), type of outcomes, and adjusted variables.

2.3. Assessment of Methodological Quality

We used the Newcastle-Ottawa Scale (NOS) in order to assess the methodological quality of the cohort studies included in the current meta-analysis [32]. The NOS comprises eight items and provides a scoring system ranging between 0 and 9. We classified individual cohort studies as having high or low quality based on the mean score.

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2.4. Main and Subgroup Analyses

We investigated the association between smoking and the risks of FLD for the main analysis. We also conducted subgroup meta-analyses by type of study (prospective or retrospective cohort study), region (Europe, Asia, or US), type of FLD, gender (male or female), follow-up period (<5 years or >5 years), and study quality (high or low quality).

2.5. Statistical Analysis

A combined OR, RR, or HR with its corresponding 95% CIs was calculated utilizing the adjusted OR, RR, or HR and their respective 95% CIs from each study that reported the association between smoking and the risk of FLD. The DerSimonian and Laird method [33] was employed, opting for a random-effects model due to the diverse populations across studies. Heterogeneity was evaluated using Higgins I^2 computed as follows:

$$I^2 = 100\% \times (Q - df)/Q,$$

where Q is Cochran's statistic for heterogeneity, and df is degrees of freedom [32]. I^2 values range between 0% (no heterogeneity) and 100% (maximal heterogeneity) [32]. Publication bias was assessed using both Beg**g'**s funnel plot and Egge**r'**s test. We used the STATA SE version 15.1 software package (StataCorp, College Station, TX, USA) for statistical analyses.

3. Results

3.1. Study Selection

Figure 1 shows the diagram of identifying relevant studies. A total of 806 studies were identified by the initial search of PubMed and EMBASE databases by using keywords. After excluding duplicates, 622 articles were screened based on the review of each title and abstract. After excluding 546 articles according to the predetermined selection criteria, 76 full-text articles were reviewed and assessed for eligibility. Among them, 56 articles were excluded for the following reasons: not relevant (n = 46); not cohort studies (n = 4); identical population (n = 4); and insufficient data (n = 2). The final analysis included 20 cohort studies (Figure 1) [11–30].

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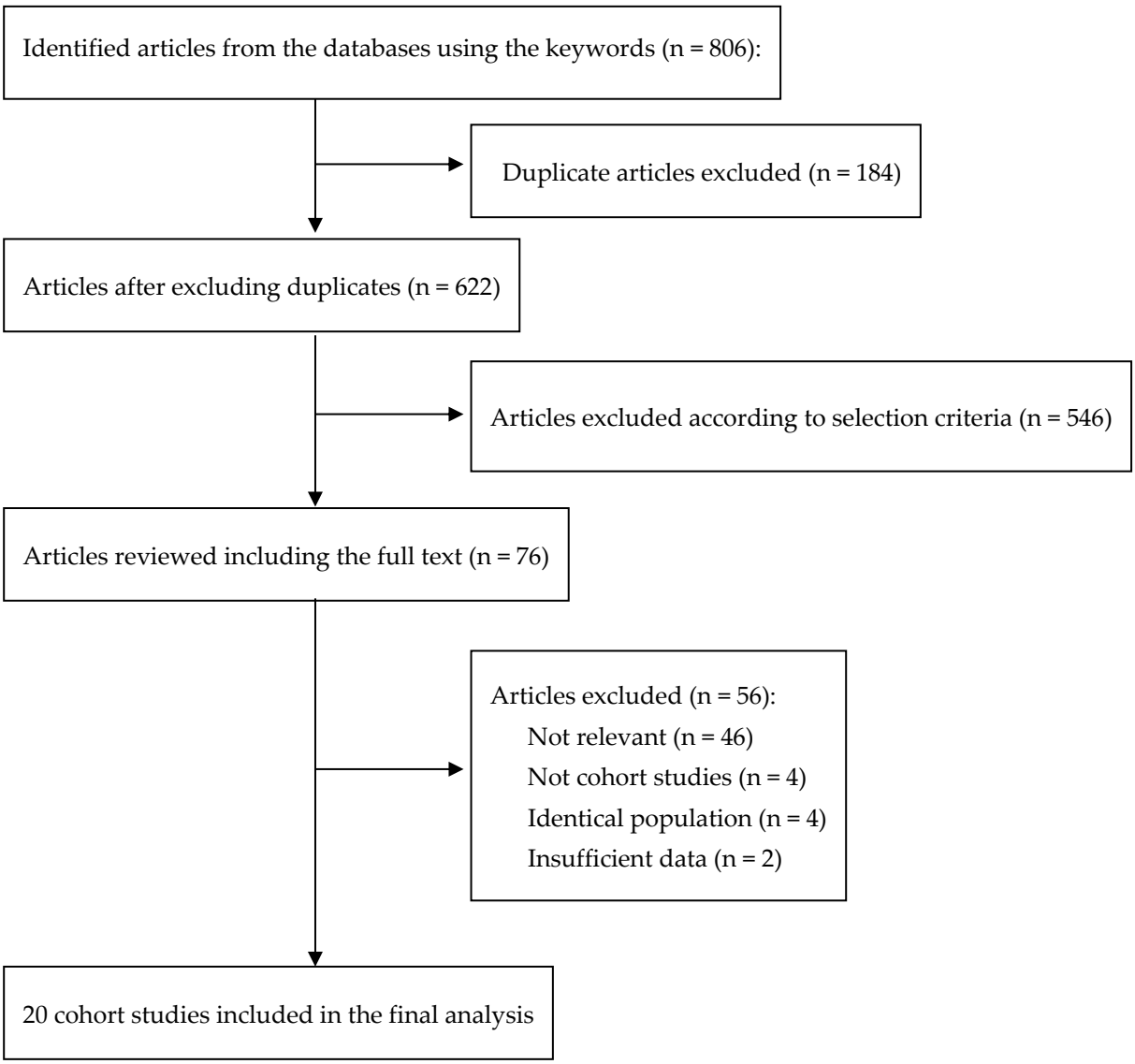

Figure 1. Flow diagram of identifying relevant Studies.

3.2. General Characteristics of Included Studies

Table 1 shows general characteristics of the cohort studies included in the final analysis. Eight studies were conducted in Europe, 10 were conducted in Asia, and the remaining two studies were conducted in the US. Types of study designs are prospective cohort studies (n = 5), retrospective cohort studies (n = 6), and cross-sectional surveys based on cohort studies (n = 9). Types of outcomes are FLD (n = 6) and NAFLD (n = 14).

3.3. Methodological Quality of Studies

The average score of the 11 prospective and retrospective cohort studies assessed using the NOS was 7.5 (Table 2). Each study's methodological quality was categorized as either high (a score of ≥8) or low (a score of <8). Out of the 11 studies, six were classified as high-quality studies, while the remaining 5 were categorized as low-quality studies.

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Table 1. General characteristics of the studies Included in the final analysis (n = 20).

Study	Region	Type of study	Gender	Study participants (% of men)	Comparison	Odds ratio, relative Risk, or hazard ratio, and 95% confidence interval	Outcomes	Adjusted variables
2010 Tsuneto [11]	Asia	Prospective	Both	1,635 atomic bomb survivors who underwent biennial examinations in Nagasaki without NAFLD at baseline	Ex-smoker or current smoker vs. none	0.92 (0.64-13.4)	FLD	Age, sex, BMI, DM, HTN, dyslipidemia, drinking habits, and atomic radiation dose
2011 Hamabe [12]	Asia	Retrospective	Both	1,560 subjects without NAFLD who underwent a complete medical health checkup at the Kagoshima Kouseiren Medical Healthcare Center	Cigarette smoking vs. no smoking	1.44 (0.86-2.42)	NAFLD	Age, sex, obesity, HTN, dyslipidemia, dysglycemia, and alcohol intake
2015 Koch [13]	Europe	Cross-sectional	Both	747 official population registeries in Kiel	Cigarette smoking vs. no smoking	1.14 (0.71-1.82)	FLD	Age, sex, years of education, total energy intake, physical activity, and waist circumference
2015 Suomela [14]	Europe	Cross-sectional	Both	3,592 Young Finns	Current smoker vs. none	2.56 (1.18-5.52)	FLD	Age, sex, BMI, and waist circumference

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2015 Zhang [15]	Asia	Prospective	Both	15,791 health check-up participants at the Center for Health Management of Shandong Provincial Qianfoshan Hospital and Shandong Provincial Hospital	Current smoker vs. none	1.03 (0.95-1.11)	NAFLD	Baseline Mets status, sex, age, diet, smoking status, and regular exercise
2017 Kim [16]	Asia	Retrospective	Both	17,028 health-screening exam participants at the Center for Health Promotion of the Samsung Medical Center, South Korea	Current smoker vs. none	0.96 (0.81-1.15)	NAFLD	Age, sex, body mass index, year of screening exam, alcohol intake, regular exercise, and education level
2017 Liu [17]	Asia	Cross-sectional	Male	9,432 DFTJ cohort study among retirees of Dong feng Motor corporation	Current smoker vs. none	1.52 (1.22-1.88)	NAFLD	Age, body mass index, waist circumference alcohol intake, DM, HTN, dyslipidemia, and past history of CHD
2017 van den Berg [18]	Europe	Cross-sectional	Both	37,496 Framework of the Lifelines Cohort Study	Current smoker vs. none	1.32 (1.21-1.43)	FLD	Age, sex, Hemoglobin, ALT/ALP/Albumin, HBA1c, Type 2 DM, dyslipidemia, and past history of CHD
2018 Bayerl [19]	Europe	Cross-sectional	Both	1,282 persons from Cooperative Health Research in German region	Ex-smoker or current smoker vs. none	0.56 (0.27-1.17)	FLD	Age, sex, DM, and alcohol intake

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2018 Okamoto [20]	Asia	Retrospective	Both	7,905 persons who underwent health checkup at Ehime General Health Care Association	Current smoker vs. none	2.25 (1.10-4.38)	FLD	Age, sex, BMI, DM, HTN, CVD, dyslipidemia, and snacking habit
2018 Okamura [21]	Asia	Retrospective	Both	29,555 medical examination program at Murakami Memorial Hospital using the NAGALA (NAFLD in the Gifu Area, Longitudinal Analysis) database	Current smoker vs. none	0.88 (0.78-0.99)	NAFLD	Age, sex, BMI, ALT, triglycerides, exercise habit, alcohol consumption, systolic blood pressure, fasting plasma glucose, and uric acid
2018 Wang [22]	Asia	Prospective	Both	10,375 participants from community residents in the Jiading District of Shangia	Current smoker or quit<12mo vs. none	1.11 (0.78-1.56)	NAFLD	Age, sex, alcohol consumption, education, and HOMA-IR
2019 Jung [23]	Asia	Prospective	Both	199,468 persons who underwent health checkup at Kangbuk Samsung Health Study	Ex-smoker or current smoker vs. none	Men: 1.15 (1.12-1.18) Women: 1.14 (1.03-1.27)	FLD	Age, sex, BMI, DM, HTN, dyslipidemia, alcohol drinking, education level, physical activity, waist circumference, and laboratory test
2019 van den Berg [24]	Europe	Cross-sectional	Both	6,132 participants of the prevention of Renal and Vascular End-stage Disease cohort study	Current smoker vs. none	1.24 (1.05-1.46)	NAFLD	Age, sex, BMI, DM, HTN, dyslipidemia, alcohol drinking, estimated GFR, urine albumin excretion, use of antihypertensive medication, glucose lowering drugs, lipid

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								lowering drugs, and HOMA-IR
2020 Chen [25]	US	Cross-sectional	Both	154 World Trade Center participants in NIOSH	Current smoker vs. none	0.41 (0.17-0.99)	FLD	Age, sex , Ethnicity, BMI, DM,HTN,COPD, and membership in the WTC
2020 Okamura [26]	Asia	Retrospective	Both	13,728 population-based longitudinal study of participants in a medical checkup program at Asahi University Hospital	Current smoker vs. none	1.16 (0.88-1.52)	NAFLD	Age, aspartate aminotransferase, fasting plasma glucose, triglyceride to high-density lipoprotein cholesterol ratio, systolic blood pressure, alcohol consumption, and exercise.
2020 Takenaka [27]	Asia	Cross-sectional	Both	8,297 health check-up participants at Yodogawa Christian Hospital	Current smoker vs. none	1.31 (1.17-1.47)	NAFLD	Age, sex, presence of metabolic syndrome, and light alcohol consumption
2021 Zhang [28]	Asia	Prospective	Both	16,839 participants who received the Kailuan Group's detailed and thorough medical examination at Tangshan City, China	Current smoker vs. none	1.15 (1.06-1.25)	NAFLD	Age, sex, marital status, working type, education level, physical activity, systolic blood pressure , lipid profile, CRP, and Cr

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2023 Jeong [29]	Asia	Retrospective	Both	296,033 in NHIS of Korea	Current smoker vs. none	1.64 (1.39-1.94)	FLD	Age, sex, household income, BMI, HTN, DM, HL, physical activity, and Charlson comorbidity index
2023 Sadeghianpour [30]	Asia	Cross-sectional	Both	180,000 Iranian adults in Hoveyzeh Cohort Study	Current smoker vs. none	0.63 (0.50-0.79)	FLD	Age, sex, area, physical activity, Energy intake Household income, DM, HL, Education level, wealth status, and skill level

Abbreviations: NAFLD, non-alcoholic fatty liver disease; FLD, fatty liver disease; DMC, Dong feng Motor Corporation; BMI, body mass index; DM, Diabetes Mellitus; HTN, Hypertension; HL, Hyperlipidemia; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NIOSH, National Institute of Occupational Safety and Health ; NHIS, National Health Insurance Service ; HOMA-IR, homeostasis model assessment of insulin resistance ; GFR, glomerular filtration rate.

Table 2. Methodological quality of studies assessed by the Newcastle-Ottawa Scale (n = 11).*.

Studies	**Selection**				**Comparability**	**Exposure**			**Total score**
	1	**2**	**3**	**4**	**1**	**1**	**2**	**3**	
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest not present at start of the study**	**Comparability of cohorts**	**Assessment of outcome**	**Adequate follow-up period for outcome of interest**	**Adequacy of follow-up of cohorts**	
2010 Tsuneto	0	1	1	1	2	1	1	0	7
2011 Hamabe	1	1	0	1	2	1	1	0	7
2015 Zhang	1	1	0	1	2	1	1	1	8
2017 Kim	1	1	0	1	2	1	1	1	8

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2018 Okamoto	1	1	0	1	2	1	1	1	8
2018 Okamura	1	1	0	1	2	1	1	0	7
2018 Wang	1	1	1	1	2	1	1	0	8
2019 Jung	1	1	0	1	2	1	1	0	7
2020 Okamura	1	1	0	1	2	1	1	1	8
2021 Zhang	1	1	0	1	2	1	1	0	7
2023 Jeong	1	1	0	1	2	1	1	1	8

*Among the 20 cohort studies included in the final analysis, cross-sectional surveys were excluded for the assessment of methodological quality. The average score of all the prospective and retrospective cohort studies is 7.5.

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3.4. Association Between Smoking and Risk of FLD

In the meta-analysis of all the included studies, smoking was associated with an increased risk of FLD (OR/RR/HR = 1.14; 95% CI, 1.05 – 1.24; n = 20) (Figure 2).

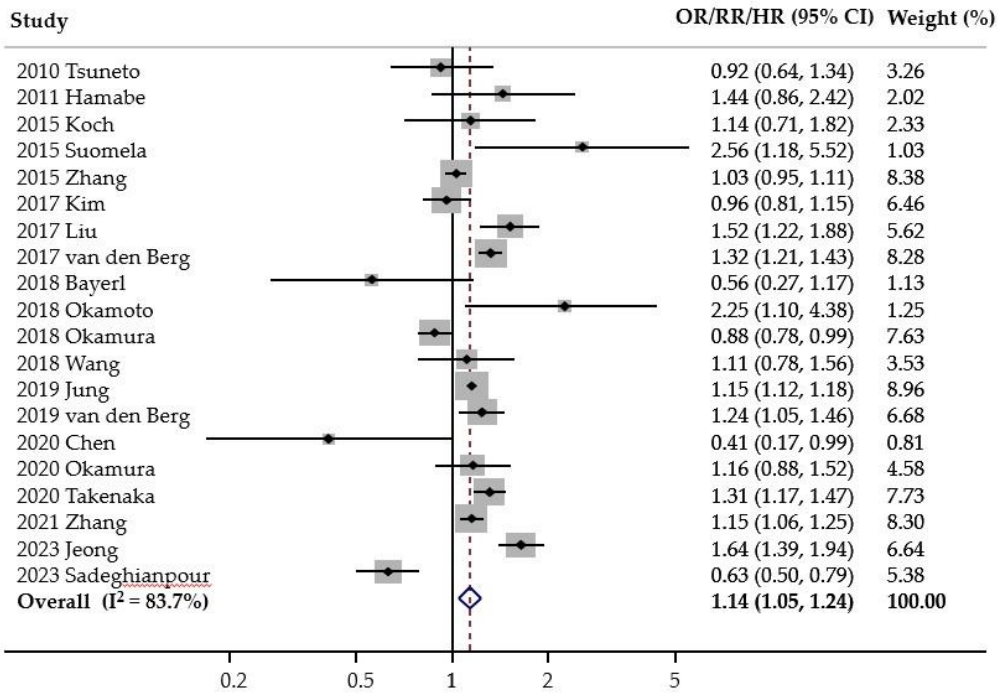

Figure 2. Smoking and risk of fatty liver disease in the meta-analysis (n = 20). OR, odds ratio; RR, relative risk; HR, hazard ratio; CI, confidence interval.

3.5. Subgroup Meta-Analyses

Table 3 shows the associations between smoking and the risk of FLD in the subgroup meta-analysis by various factors. In the subgroup meta-analysis by study design, smoking increased the risk of FLD in prospective cohort studies (HR = 1.15; 95% CI 1.05 – 1.18; n = 5), but not in retrospective cohort studies (OR/RR = 1.23; 95% CI 0.94 – 1.62) and cross-sectional surveys (OR/RR = 1.12; 95% CI 0.92-1.46; n = 9). In the subgroup meta-analysis by study region, smoking was significantly associated with an increased risk of FLD in in Europe (OR/RR/HR = 1.32; 95% CI 1.16 – 1.50; n = 8), but not in Asia (OR/RR/HR = 1.03; 95% CI 0.91 – 1.18; n = 10) and the US (OR/RR/HR = 0.75; 95% CI 0.28 – 2.06; n = 2). In the subgroup meta-analysis by gender, which data are available only for Asian studies, smoking significantly increased the risk of FLD in men (OR/RR/HR = 1.15; 95% CI 1.06 – 1.25; n = 4), while there was no significant association between them in women (OR/RR/HR = 1.12; 95% CI 0.94 – 1.34; n = 4).

Table 3. Association between smoking and fatty liver disease in subgroup meta-analysis by various factors.

Factor	No. of studies	RR (95%CI)	Heterogeneity I^2 (%)
All studies	20	1.14 (1.05-1.24)*	83.7
Type of cohort study			
Prospective	5	1.15 (1.05-1.18)*	51.7
Retrospective	6	1.23 (0.94-1.62)	88.4

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Cross-sectional	9	1.12 (0.92-1.36)	85.2
Region			
Europe	8	1.32 (1.16-1.50)*	82.1
Asia	10	1.03 (0.91-1.18)	83.5
US	2	0.75 (0.28-2.06)	79.5
Type of fatty liver disease			
Fatty liver disease	6	1.27 (1.01-1.59)*	72.7
Non-alcoholic fatty liver disease	14	1.09 (1.00-1.19)*	83.2
Gender (All from Asia)			
Men	4	1.15 (1.06-1.25)*	71.2
Women	4	1.12 (0.94-1.34)	47.8
Follow-up period			
<5 years	3	1.44 (0.95-2.13)	93.0
>5 years	7	1.08 (0.98-1.19)	70.9
Quality of study†			
High	6	1.16 (0.94-1.42)	85.3
Low	5	1.07 (0.95-1.20)	67.1

*Indicates a significant association. RR, relative risk; CI, confident interval. † Study quality was assessed based on the Newcastle-Ottawa Scale.

Regardless of type of FLD, smoking consistently increased the risk of FLD. On the contrary, subgroup meta-analyses by follow-up period and study quality showed no significant association between smoking and the risk of FLD.

3.6. Publication Bias

Both the Begg's funnel plots (Figure 3) and Egger's test (P = 0.29) did not show publication bias.

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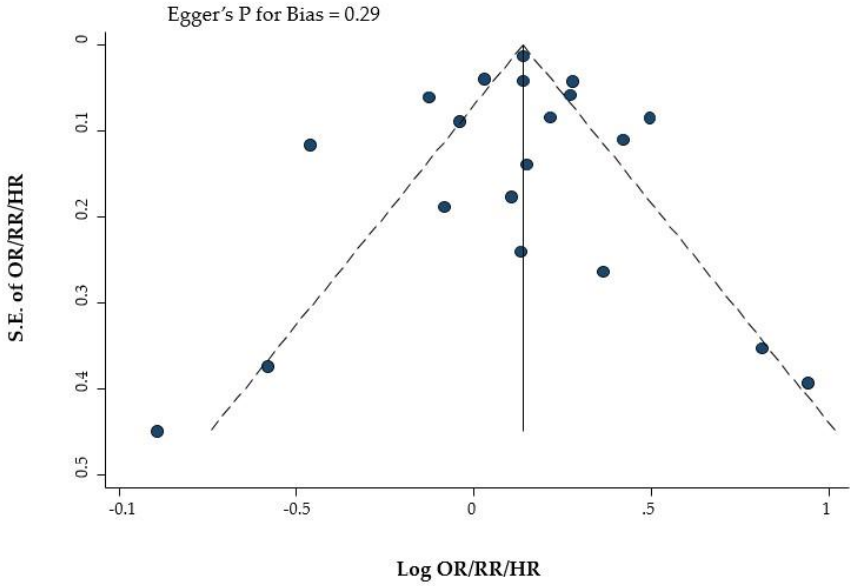

Figure 3. Begg's funnel plot and Egger's test to test publication bias (n = 20). OR, odds ratio; RR, relative risk; HR, hazard ratio; S.E, standard error.

4. Discussion

In this meta-analysis of cohort studies, we found that smoking was significantly associated with an increased risk of FLD. In the subgroup meta-analysis by study design, smoking increased the risk of FLD in prospective cohort studies, but not in retrospective cohort studies and cross-sectional surveys. Also, smoking was significantly associated with an increased risk of FLD in Europe, but not in Asia and the US. Interestingly, in the subgroup meta-analysis by gender in Asians, smoking significantly increased the risk of FLD in men, while there was no significant association between them in women.

There are several possible biological mechanisms that could explain the increased risk of FLD by smoking. First, Yuan et al.'s study demonstrated that smoking stimulated lipid accumulation in hepatocytes in mice and cultured hepatocytes [9]. When mice and cultured hepatocytes were exposed to sidestream whole smoke, lipid accumulation was increased by modulating the activity of AMP-activated protein kinase and sterol response element binding protein-1, which are critical molecules in lipid synthesis [9]. Second, smoking has the potential to induce insulin resistance, which leads to the development of NAFLD [34,35]. A study revealed that cigarette consumption is correlated with degree of insulin resistance in smokers [36]. Also, a study in biopsy-proven NAFLD patients and health control subjects showed that homeostasis model assessment of insulin resistance (HOMA-IR) levels were significantly higher in the NAFLD patients [35]. Insulin resistance induced by smoking could enhance hepatic fat accumulation through increasing free fatty acid delivery to the liver and through hyperinsulinemia to contribute to triacylglycerol accumulation in the liver [37]. Third, nicotine in tobacco smoke could increase the release of norepinephrine and epinephrine, which could affect thermogenesis in adipose tissue, leading to the increased lipolysis and the subsequent recycling of fatty acids into triglycerides [38]. Consequently, it may contribute to the development of NAFTD. Lastly, adiponectin could inhibit liver fat deposition, and gluthathione peroxidase (GPx) could reduce lipid and hydrogen peroxide [39]. Thus, it has been suggested that cigarette smoking in combination with single-nucleotide polymorphisms in the adiponectine gene and GPx1 gene mutation could contribute to the development of NAFLD [39].

Previously, a meta-analysis of 12 observational studies by Akhavan et al. has already reported that smoking moderately increased a risk NAFLD [31]. However, it included only two cohort studies, and the remaining studies were seven cross-sectional and three case-control studies. Although it is

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possible to combine different study designs such as cross-sectional, case-control, and cohort studies when conducting a meta-analysis, conducting subgroup meta-analyses by study designs is crucial and useful because there could be discrepancies in findings between different study designs. Also, based on the 'levels of evidence pyramid', cohort studies give us a higher level of evidence than cross-sectional and case-control studies [40]. Akhavan et al. performed subgroup meta-analyses by study designs and reported significant increased risks of NAFLD by smoking in all the subgroup meta-analyses by each study design such as cross-sectional, case-control, and cohort studies [31]. However, they included just two cohort studies, which are not enough to confirm the association between smoking and the risk of NAFLD. In the current meta-analysis, we included 11 cohort studies involving five prospective and six retrospective cohort studies and nine cross-sectional surveys based on cohort studies. Thus, our findings would provide more clear and convincing evidence on this topic.

A notable strength lies in the subgroup meta-analyses by various factors. We confirmed a significantly increased risk of FLD in prospective cohort studies, which are generally considered as having a higher level of evidence than retrospective cohort studies and cross-sectional studies although retrospective and cross-sectional studies in the current analysis showed no significant association between smoking and the risk of FLD.

Interestingly, a significantly increased risk of FLD by smoking was observed in the studies conducted only in Europe, but not Asia and the US. We included just two studies conducted in the US that are not enough to draw a definite conclusion. Thus, more studies are required to confirm the association for people in the US. On the contrary, the number of studies conducted in Asia is sufficient to draw a conclusion. We do not have exact reasons why there were discrepancies in findings on this topic between Europeans and Asians. However, we have a potential explanation. A misclassification of Asian women's smoking status might lead to a non-significant association between smoking and the risk of FLD in the current analysis. Unlike adult men, smoking rates among adult women have been known to be very low (<10%) in South Korea, China, and Hong Kong [41,42]. One of the main reasons of the low smoking prevalence in Asian women is under-reporting. The accuracy of smoking rates self-reported by women in Asian countries has been doubted because social repression and disapproval of women's smoking might make women reluctant to report their smoking status [43–45]. A study using the Korean National Health and Nutrition Examination Survey reported that among the cotinine-verified smokers, about 60% of women classified themselves as non-smokers in a self-report survey [42]. When we performed the subgroup analysis by gender, smoking significantly increased the risk of FLD in Asian men, although there was no significant association between them in Asian women. Thus, the discrepancy in findings between Europeans and Asians might be mainly attributable to a misclassification of Asian women's smoking status, but not race or ethnicity.

Despite the strengths, there are several limitations in this study. First, we included only five prospective cohort studies. Out of 20 cohort studies included in the current analysis, most studies were retrospective cohort studies and cross-sectional surveys based on cohort studies. As mentioned above, because prospective cohort studies give us a higher level of evidence than retrospective cohort studies and cross-sectional studies, our findings should be confirmed by further prospective cohort studies. Second, most studies measured smoking status based on a self-report. As discussed earlier, self-reported measure of smoking status may lead to under-reporting and a misclassification of smoking status, which could result in biased conclusions. Thus, further studies with biochemical validation of smoking status such as urinary cotinine levels are warranted to confirm our findings. Last, we were unable to investigate the association between the number of cigarettes smoked and the risk of FLD due to a lack of data reported in each study.

In summary, we found that smoking increases the risk of FLD in the meta-analysis of cohort studies. In addition to well-known risk factors of FLD such as obesity and alcohol consumption, clinicians should recommend smoking cessation for the management of FLD.

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