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# Impact of smoking cessation on non-alcoholic fatty liver disease prevalence: a systematic review and meta-analysis

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## ABSTRACT

**Objectives** The negative effects of smoking on numerous cardiovascular and metabolic diseases have been widely acknowledged. However, the potential effect of smoking cessation is relatively unelucidated. The objective of this study is to explore whether the prevalence of non-alcoholic fatty liver disease (NAFLD) in former smokers differs from the prevalence in current smokers.

**Design** Systematic review and meta-analysis.

**Data sources** Four databases, that is, PubMed, Web of Science, Journal@Ovid and Scopus were searched from inception to 31 January 2023.

**Eligibility criteria** Population-based cross-sectional studies, including the baseline data of cohort studies with identified NAFLD diagnostic methods, and smoking status (current smoker or former smoker) of participants were included.

**Data extraction and synthesis** Two reviewers independently extracted the data including cigarette smoking status, country/region of studies, NAFLD diagnostic methods, sex, the average age and body mass index (BMI) of NAFLD participants and assessed the risk of bias with Agency for Healthcare Research and Quality (AHRQ) methodology checklist. Risk ratio (RR) of NAFLD prevalence in former smokers was pooled using the random-effects model.

**Results** 28 studies involving 4 465 862 participants were included. Compared with current smokers, the RR of overall NAFLD prevalence in former smokers was 1.13 (95% CI: 1.08 to 1.19, prediction interval: 0.92–1.39). This result persisted after adjustment for diagnostic methods, country/region, sex, age and BMI. Sensitivity analysis and risk of bias assessment indicated a stable conclusion.

**Conclusions** NAFLD prevalence in former smokers was at least not lower than that in current smokers and was partially related to increased BMI after smoking cessation, indicating that smoking cessation was possibly not a protective factor against NAFLD. Although the meta-analysis based on cross-sectional studies cannot conclude the causal relationships between smoking cessation and NAFLD onset, the potential onset of NAFLD associated with smoking cessation should be highlighted.

**PROSPERO registration number** CRD42023394944.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The finding was based on cross-sectional studies, which cannot conclude the causal relationships between smoking cessation and non-alcoholic fatty liver disease onset.
⇒ This systematic review and meta-analysis covered studies from most regions, however, data from Africa and Oceania were absent from this study.
⇒ Smoking status in most studies included was self-reported, leading to inevitable recall bias.

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is regarded as the hepatic manifestation of metabolic syndrome and is associated with various diseases including obesity, dyslipidaemia, hypertension and diabetes.[1] The prevalence of NAFLD is a tremendous socioeconomic burden, for example, about 100 million individuals in the USA may have NAFLD around 2030,[2] thus the prevention and management of NAFLD are of great importance. One of the most effective interventions for NAFLD is lifestyle changes, which include weight loss through a combination of diet and exercise and adopting a less sedentary lifestyle.

Numerous population-based cross-sectional studies reported the prevalence of NAFLD. Since the invasiveness of biopsy prevents its application in population-based screening programmes, various methods are used to identify NAFLD in population-based studies including calculations based on biochemical indicators and anthropometric indices, such as fatty liver index (FLI) and hepatic steatosis index (HSI) and medical imaging approaches such as ultrasound, CT, MRI and controlled attenuation parameter (CAP).

Smoking affects a large proportion of the global population, for example, approximately 34 million people in the USA smoke cigarettes,[3] which is one of the leading causes of preventable death.[4] Numerous studies have comprehensively elucidated the adverse effects of current smoking on many diseases, such as cardiovascular diseases[5] and

metabolic diseases including NAFLD and liver fibrosis.[6 7] Currently, heterogeneous findings about the relationship between smoking status and NAFLD have been reported. It is to some extent acknowledged that smoking cessation can be associated with NAFLD development,[6] and a cohort study in Japan found that smoking cessation was independently associated with NAFLD development.[8] However, a previous study showed that smoking cessation may be a protective factor against NAFLD via analysing a Korean database (KNHANES 2019–2020).[9] Because of these heterogeneous findings, the potential relationship between smoking cessation and NAFLD worldwide remains unclear. The aim of this systematic review and meta-analysis of population-based studies is to explore whether smoking cessation influences NAFLD prevalence by comparing NAFLD prevalence between former and current smokers.

## METHODS

### Protocol and registration

Population-based cross-sectional studies and the baseline data of cohort studies were included in this study. Because the difference in the means of NAFLD diagnosis is a potential source of heterogeneity, we only included studies with identified diagnostic methods for analyses. The protocol of this systematic review and meta-analysis has been registered previously.[10] The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (online supplemental file 1) and PRISMA-S extension (online supplemental file 2) were followed.

### Literature search strategy

In brief, we screened PubMed, Web of Science, Journals@Ovid (All Ovid Journals) and Scopus databases from inception to 31 January 2023 (for search in PubMed, weekly email alert for updates was performed until 23 September 2023) and retrieved 3032 studies by using the keywords of NAFLD, smoking and their synonyms, referring to a previous study.[11] For example, the search strategy in PubMed was ('smoke' (Title/Abstract) OR 'smoking' (Title/Abstract) OR 'tobacco' (Title/Abstract) OR 'cigarette' (Title/Abstract)) AND ('NAFLD' (Title/Abstract) OR ('liver' (Title/Abstract) AND 'steatosis' (Title/Abstract)) OR 'fatty liver disease' (Title/Abstract)), without additional filters or limits. The full search strings for all databases were attached (online supplemental file 3). References of included articles were also screened manually. There were no language limitations to the search. Moreover, we searched clinical trial registries ( ClinicalTrials.gov) to identify ongoing trials. We also searched possible grey literature on Microsoft Bing (on 23 September 2023), and the first 20 results were selected and screened. Two authors (SZ and ZL) independently

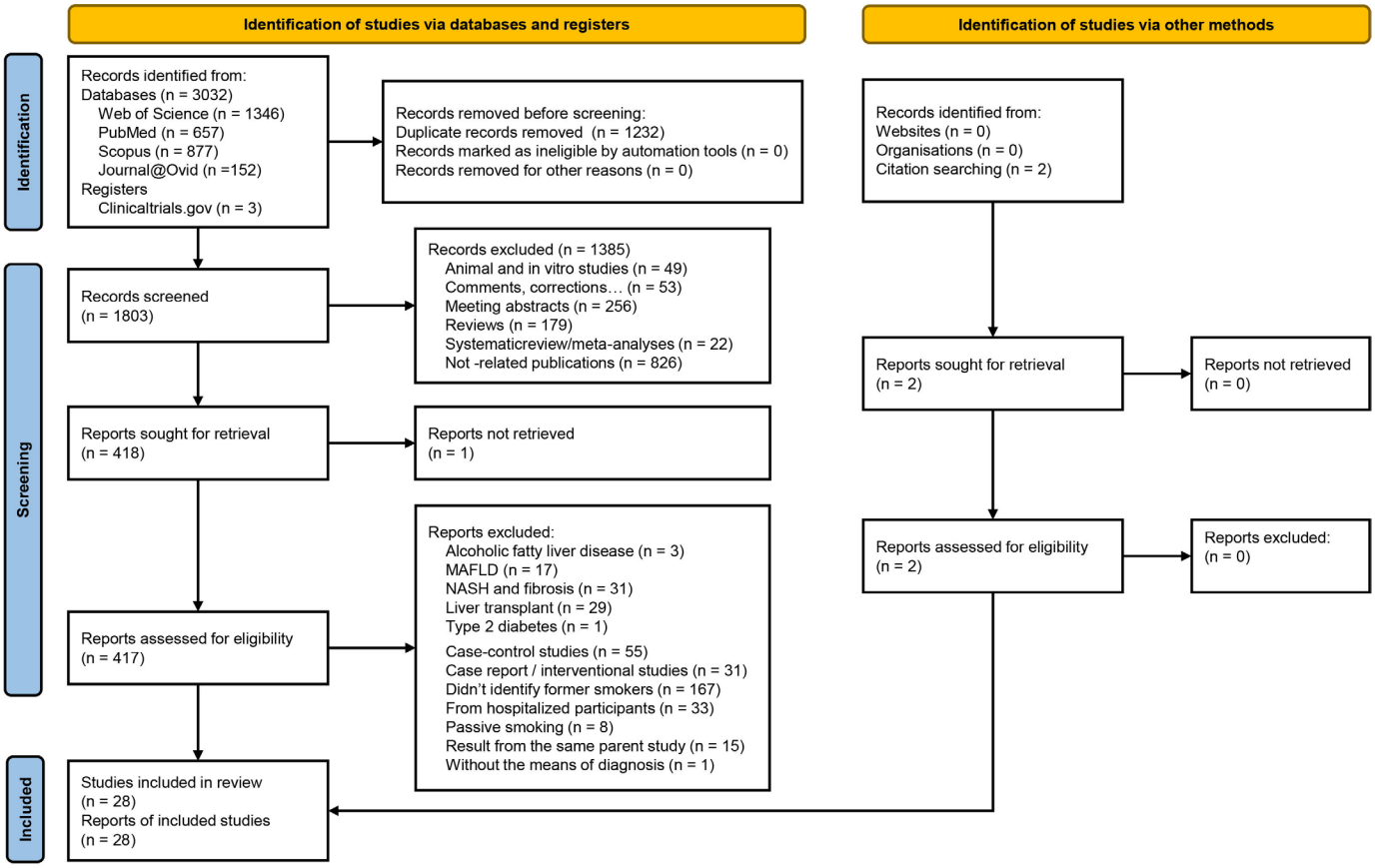


**Figure 1** Flowchart of literature search and selection process. MAFLD, metabolic dysfunction-associated fatty liver disease; NASH, non-alcoholic steatohepatitis.

screened and retrieved each study, and disagreements were resolved with another two authors (YD and WZ) by consensus. The screening and retrieving process for all articles was conducted in the Zotero 6.0.27.

### Study selection criteria

Duplicate items, including articles interpreting the results of the same parent database, were removed through Zotero JavaScript and then manually. Eligibility criteria for inclusion in this systematic review and meta-analysis are below. (1) The study must state identified NAFLD diagnostic methods, including but not limited to ultrasound, CT, MRI, FLI, etc. (2) The study must contain the smoking status of participants (current smoker or former smoker) reported by the participants through a questionnaire or interview, and smoking status obtained from hospital information system is also acceptable. (3) The study must be a population-based cross-sectional study, including baseline data of the cohort study. Irrelevant article types, including comments, meeting abstracts, reviews, systematic reviews/meta-analyses and articles focused on animal and in vitro experiments were excluded. Moreover, other heterogeneous hepatic steatosis diseases, including alcoholic fatty liver disease and metabolic dysfunction-associated fatty liver disease (MAFLD) were excluded because of different diagnosis standards. Studies considering participants with non-alcoholic steatohepatitis (NASH), fibrosis and type 2 diabetes were excluded because of the existing known relationship between smoking and these diseases.[6 12] Cross-sectional studies based on hospitalised patients were excluded because of the considerable non-response bias of asymptomatic cases. Two authors (SZ and ZL) independently selected studies, and disagreements were resolved with another two authors (YD and WZ) by consensus.

### Data extraction process

For included studies, the first author, publication year, number of NAFLD and non-NAFLD participants in current smoking and former smoking groups, means of NAFLD diagnosis, country where the study conducted, the average age and BMI of NAFLD participants, sex difference and other data required to complete methodological quality and risk of bias assessment were collected. Two authors (QY and HZ) independently collected data of studies included in this meta-analysis, and any disagreements were discussed with another two authors (SZ and ZL) until a consensus was reached. All the data were collected and stored through Microsoft Office Excel 2019.

### Methodological quality and risk of bias assessment

The Agency for Healthcare Research and Quality (AHRQ) methodology checklist[13 14] was used to evaluate the quality of the cross-sectional studies across 11 domains. Score '0' is attributed to domains considered as 'No' or 'Unclear' and score '1' for domains considered as 'Yes'. Two authors (SZ and ZL) independently assessed the quality of the included studies. Disagreements were resolved by discussion with another two authors (YD and WZ). Funnel plots and the arcsine-Thompson test were used to assess the publication bias because the arcsine-Thompson test works well particularly when heterogeneity is high.[15]

### Statistical analysis

Since the high methodological heterogeneity of the included studies, that is, different means of NAFLD diagnosis and country/region of studies, the random-effects model was used to calculate the overall risk ratio (RR) and 95% CI. Mantel-Haenszel method was applied, and the DerSimonian-Laird estimator was chosen to estimate the between-study variance for the random-effects model of dichotomous outcomes according to the Cochrane Handbook[16] and the manual of meta package.[17] Subgroup analyses were performed based on the means of NAFLD diagnosis, the region in which the study was conducted, the average age and BMI of NAFLD participants and sex. Post hoc meta-regression analysis through a mixed-effects model was also used to identify the origin of heterogeneity, with covariates including the average age and BMI of NAFLD participants, NAFLD diagnoses and regional differences. There was no imputation for missing data. Cochran's Q-test was conducted to determine the residual heterogeneity in meta-regression analysis by using the metafor package. In addition, we performed a sensitivity analysis by using the leave-one-out method. The statistical analysis was performed by using meta[17] and metafor[18] packages through R 4.1.3 (www.r-project.org).

### Patient and public involvement

None.

## RESULTS

### Study selection process

After removing duplicate items, 1802 results were remained. Animal and in vitro studies (n=49), comments (n=53), meeting abstracts (n=256), reviews (n=179), systematic review/meta-analyses (n=22) and other irrelevant publications (n=826) were excluded. Studies focused on alcoholic fatty liver disease (n=3), MAFLD because of different diagnosis standards (n=17), NASH and fibrosis (n=31), patients with liver transplantation (n=29) and type 2 diabetes (n=1) were also excluded. Cross-sectional studies based on hospitalised patients (n=33) were excluded. Case–control studies (n=55), case reports and interventional studies (n=31) were also excluded. Studies focused on passive smoking (n=8), did not identify former smokers (n=167) and did not specify the diagnostic methods[19] (n=1) were also excluded. Another 15 articles interpreting the results of the same parent database were also excluded. A study registry considering weight gain after smoking cessation and NAFLD was found via Clinicaltrials.gov,[20] however, there was no publication or data available. There was no additional grey literature found. Finally, 28 studies were included in the systematic review and meta-analysis (figure 1).

Table 1 Characteristics of the included studies

| Study | Participants | Diagnosis | Duration | Country | Age_NAFLD | BMI_NAFLD |
|---|---|---|---|---|---|---|
| Pettinelli (2023)[26] | 4 397 572 | FLI | 2016–2017 | Chile | 46.3 | 33.00 |
| Evstifeeva (2022)[27] | 1591 | FLI | 2017 | Russia | 47.8 | NA |
| Hu (2022)[28] | 5505 | Ultrasound | 2004–2015 | Japan | 44.8 | 25.50 |
| Lee (2022)[29] | 2825 | NAFLD-liver fat score | 2001–2002 | Korea | 54.3 | 26.50 |
| Roh (2022)[30] | 609 | HSI | 2016–2017 | Korea | 74.0 | 26.50 |
| Truong (2022)[31] | 1368 | CAP | 2017–2018 | USA | 49.3 | 33.58 |
| Wang (2022)[32] | 1601 | Ultrasound | 2018 | China | 69.3 | NA |
| Yuan (2022)[33] | 16 308 | Ultrasound | 2018 | China | NA | NA |
| Cai (2021)[21] | 1949 | US FLI | 2003–2016 | USA | 51.9 | NA |
| Gerber (2021)[34] | 1027 | CT or MRI | 1985–1986 | USA | 50.5 | NA |
| Moon (2021)[35] | 7576 | HSI | 2008–2015 | Korea | 50.1 | 27.60 |
| Song (2021)[36] | 2520 | HSI | 2016–2018 | Korea | 46.0 | 27.60 |
| Fricker (2019)[37] | 1236 | CT or MRI | 1975–2005 | USA | 52.0 | 31.00 |
| Golabi (2019)[22] | 1213 | US FLI | 2011–2016 | USA | 52.7 | 33.61 |
| Harada (2019)[38] | 3114 | Ultrasound | 2009–2013 | Brazil | 53.0 | 28.51 |
| Hsing (2019)[39] | 637 | FLI | 2016 | China | NA | 28.50 |
| Zhou (2019)[40] | 951 | CT or MRI | 2012–2013 | China | 50.0 | 27.77 |
| Guo (2018)[41] | 628 | Ultrasound | 2013–2013 | China | 54.6 | NA |
| Rietman (2018)[42] | 335 | FLI | 2011–2013 | Netherlands | .0 | 31.05 |
| Koch (2017)[43] | 293 | CT or MRI | 2005–2007 | Germany | 64.8 | 27.75 |
| Liu (2017)[44] | 5607 | Ultrasound | 2008–2009 | China | 65.0 | 26.68 |
| Onat Altan (2015)[45] | 596 | FLI | 2003–2004 | Turkey | 53.3 | 32.77 |
| Shen (2014)[46] | 6531 | Ultrasound | 1988–1994 | USA | 54.6 | NA |
| Liu (2013)[47] | 1692 | Ultrasound | 2010 | China | NA | NA |
| Musso (2013)[48] | 68 | Ultrasound | 2004–2005 | Italy | 56.0 | 27.30 |
| Koehler (2012)[49] | 1782 | Ultrasound | 2009–2012 | Netherlands | 75.8 | 30.00 |
| Hou (2011)[50] | 386 | Ultrasound | 2008 | China | 42.9 | NA |
| Caballería (2010)[51] | 342 | Ultrasound | 2007–2008 | Spain | 58.0 | NA |

Age_NAFLD: average age of participants with NAFLD; BMI_NAFLD: average BMI of participants with NAFLD.
BMI, body mass index; CAP, controlled attenuation parameter; FLI, fatty liver index; HSI, hepatic steatosis index; NA, not applicable; NAFLD, non-alcoholic fatty liver disease.

### Descriptive analysis and pooled NAFLD prevalence in former smokers

We included 28 population-based cross-sectional studies, and 4 465 862 participants were included (table 1). Most studies identified smoking status by using self-report questionnaires or face-to-face interviews, and only one study did not illustrate the definition of smoking status. Various non-invasive diagnostic methods were used to identify NAFLD, including FLI (n=5), US FLI (n=2), HSI (n=3), NAFLD-liver fat score (n=1), ultrasound (n=12), CT/MRI (n=4) and CAP (n=1). Because an FLI score ranged of 30–60 is considered inconclusive for NAFLD in most of the included studies, patients with FLI<30 or ≥60 were analysed if the data were available.

The RR of the overall NAFLD prevalence in former smokers was 1.13 (95% CI: 1.08 to 1.19), with a prediction interval of 0.92–1.39 (figure 2), compared with those of current smokers. This finding indicated that compared with smoking persistence, smoking cessation did not decrease the prevalence of NAFLD. Therefore, smoking cessation may not be a protective factor against NAFLD.

### Methodological quality, sensitivity and risk of bias assessment

The results of the AHRQ methodology checklist for cross-sectional studies were illustrated (online supplemental figure 1A). All the studies described the source (D1) and period of studies (D3) and were population-based studies (D4). Former and current smoking status was based on self-report questionnaires, face-to-face interviews or hospital information systems in all studies, except in one study that did not clarify the criteria (D2). In 5

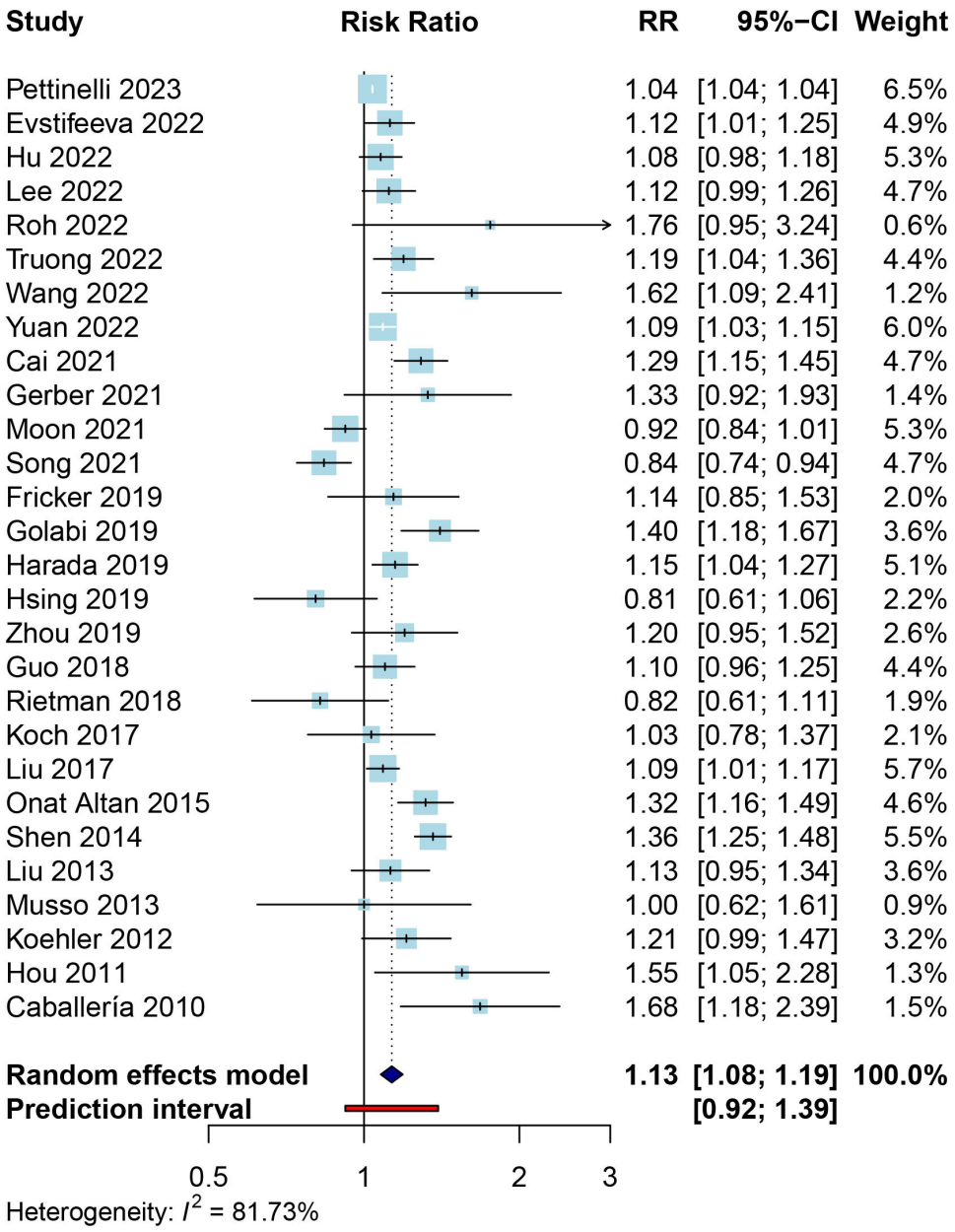


**Figure 2** NAFLD prevalence in former smokers compared with current smokers. NAFLD, non-alcoholic fatty liver index; RR, risk ratio.

of 12 studies, radiologists performing ultrasound were unaware of the participants' clinical data (D5). Furthermore, 25 of 28 studies described any assessments undertaken for quality assurance purposes (D6), 27 explained the exclusion reasons of respondents (D7), 12 described how confounding were assessed or controlled (D8), 21 explained how missing data were managed in the analysis (D9), 24 considered patient response rates and the completeness of data collection (D10) and 15 included follow-up information (D11). However, the result was regarded as relatively low-quality evidence (⨁⨁◯◯) since they were based on cross-sectional design. Subgroup analysis based on methodological quality assessment was also performed (online supplemental figure 1B), indicating that the quality difference among studies did not contribute to the overall heterogeneity, and the conclusion in subgroups of relatively low or high-quality studies remained the same.

Sensitivity analysis revealed high stability of the result (online supplemental figure 2A). The symmetric funnel plots (online supplemental figure 2B) and arcsine-Thompson test (p=0.11) indicated no significant publication bias, and the effect of the pooled result was stable.

### Subgroup analysis and meta-regression

Subgroup analyses regarding country/region differences (figure 3A), means of NAFLD diagnosis (figure 3B), average age (figure 4A) and body mass index (BMI) (figure 4C) of NAFLD participants and sex (online supplemental figure 3) were carried out, respectively. Furthermore, meta-regression analyses of country/region differences, diagnostic methods and average age

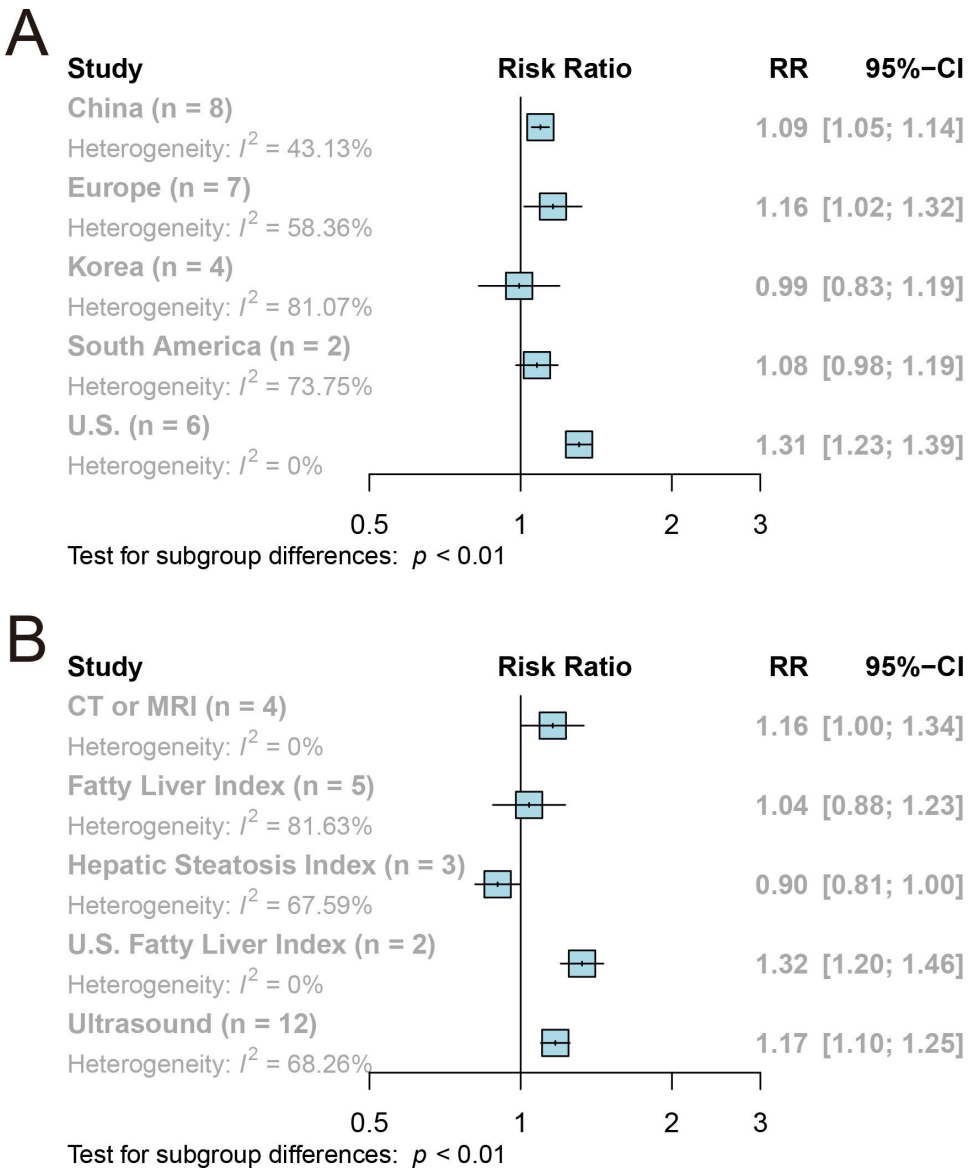


**Figure 3** Subgroup analysis based on differences in country-continent and diagnostic methods. (A) Subgroup analysis based on differences in country/continent. (B) Subgroup analysis based on differences in diagnostic methods. RR, risk ratio.

(figure 4B) and BMI (figure 4D) of the NAFLD participants were conducted.

### Subgroup analysis and meta-regression on country differences

Studies from Germany (n=1), Italy (n=1), the Netherlands (n=2), Russia (n=1), Spain (n=1) and Turkey (n=1) were combined into one group (Europe), and studies from Brazil (n=1) and Chile (n=1) were combined into one group (South America). The heterogeneity decreased in studies from China ($I^2$=43.13%), Europe ($I^2$=58.36%), South America ($I^2$=73.75%) and the USA ($I^2$=0%), compared with the heterogeneity of the overall result ($I^2$=81.73%), whereas the heterogeneity of studies from South Korea remained high ($I^2$=81.07%). There was a significant difference among these subgroups (p<0.01). Meta-regression analysis indicated that a substantial amount of heterogeneity could be attributed to the country/region differences among the studies, with a lower residual heterogeneity ($I^2$=56.58%). Compared with the heterogeneity of the overall result ($I^2$=81.73%), the country/region difference could explain a substantial amount of heterogeneity (online supplemental table 1).

### Subgroup analysis and meta-regression on means of NAFLD diagnosis

Despite the decreased heterogeneity in the CT/MRI ($I^2$=0%), HSI ($I^2$=67.59%), ultrasound ($I^2$=68.26%) and US FLI ($I^2$=0%) subgroups, the heterogeneity remained high in the FLI ($I^2$=81.63%) subgroup, indicating that the differences in diagnostic methods alone could not fully explain the heterogeneity. There was a significant difference among these subgroups (p<0.01). Meta-regression analysis indicated that a lower amount of heterogeneity could be attributed to the diagnostic differences between studies, with a relatively higher residual heterogeneity

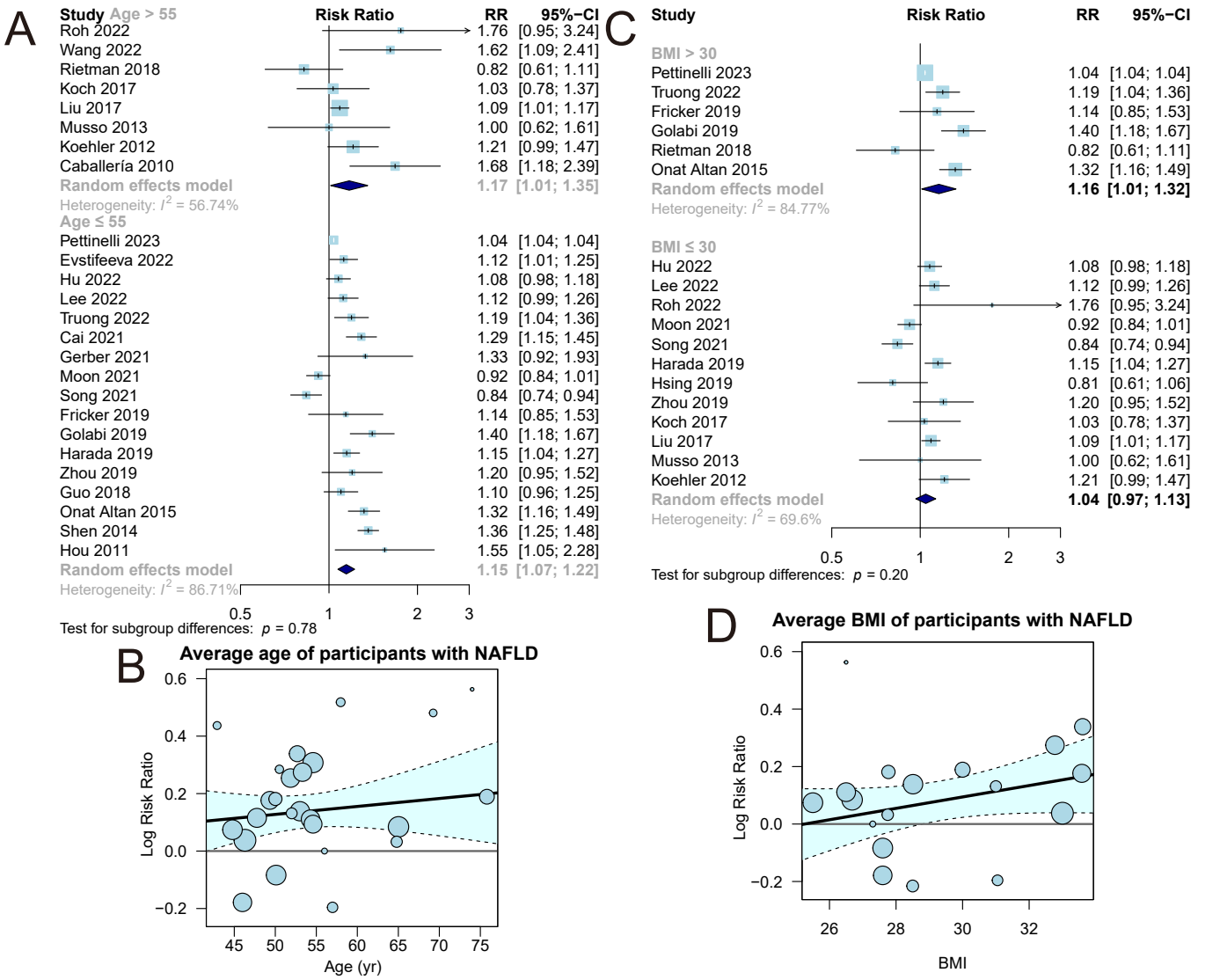


**Figure 4** Subgroup analysis and meta-regression based on average age and BMI of participants with NAFLD. (A) Subgroup analysis and (B) meta-regression based on the average age of participants with NAFLD. (C) Subgroup analysis and (D) meta-regression based on the average BMI of participants with NAFLD. BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; RR, risk ratio.

($I^2$=67.43%), indicating that the difference in diagnostic methods alone could not fully explain the heterogeneity, and the model considering differences in country/region and diagnostic methods simultaneously may explain the heterogeneity better ($I^2$=47.07%) (online supplemental table 1).

### Subgroup analysis and meta-regression on age and BMI

The lack of full access to the individual patient data (IPD) of each study precluded an IPD meta-analysis. As an alternative, we conducted subgroup analysis and meta-regression of the NAFLD risk of former smokers based on the average age and BMI of NAFLD participants, since these data were available from most of the included publications.

The RR of studies with an average age of NAFLD participants over 55 years old was 1.17 (95% CI: 1.01 to 1.35), and the RR of the average age below or equal to 55 years old was 1.15 (95% CI: 1.07 to 1.22). There was no significant difference between the two subgroups (p=0.78). Similarly, the RR of studies with the average BMI of NAFLD participants over 30 was 1.16 (95% CI: 1.01 to 1.32), and the RR of the average BMI below or equal to 30 was 1.04 (95% CI: 0.97 to 1.13). There was also no significant difference between the two subgroups (p=0.20). The result implied that the NAFLD prevalence difference between the subgroups regarding age and BMI was not large enough to impact the outcome (test for subgroup differences p=0.78 and 0.20, respectively) since the CIs overlap each other to a great extent. Smoking cessation was associated with NAFLD prevalence even after regarding age and BMI subgroups (figure 4A,C).

Either the average age or BMI of NAFLD participants was positively related to the increased NAFLD prevalence among former smokers (figure 4B,D). However, the result

suggested that the heterogeneity did not entirely originate from the age or BMI difference of NAFLD participants (online supplemental table 1).

### Subgroup analysis on sex difference

Sex is another potential source of heterogeneity. Among the 28 included studies, four studies divided the population by sex, but only one observed NAFLD onset among female former smokers (online supplemental figure 3). Compared with current smokers, the RR of NAFLD prevalence in male former smokers was 1.19 (95% CI: 1.06 to 1.34), and the prevalence in female former smokers was 0.92 (95% CI: 0.72 to 1.17). No difference was noticed in NAFLD prevalence between male and female former smokers (p=0.06), but because only one study considered female former smokers, the conclusion may not be stable.

## DISCUSSION

### Differences in country/region and diagnostic methods

Although we conducted several subgroup analyses of differences in country and diagnostic methods, the heterogeneity could not be fully explained, indicating the lack of a one-size-fits-all formula for NAFLD screening because of differences in ethnicity. To avoid the heterogeneity caused by ethnic differences, two studies included used US FLI to detect NAFLD, which is a modification of FLI, to consider ethnicity and age differences, leading to a more stable conclusion with lower heterogeneity.[21 22] Besides, the heterogeneity in the ultrasound subgroup was also relatively high, which may result from the absence of blinding methods and unified diagnostic criteria. Therefore, we executed a meta-regression including differences in ethnicity and diagnosis together, which considerably reduced the residual heterogeneity.

### BMI gain after smoking cessation

BMI gain after smoking cessation may also contribute to the higher NAFLD prevalence in former smokers. Smoking reduces body weight by increasing energy expenditure and suppressing caloric intake. Therefore, the weight gain after quitting smoking is considerable. Weight gain after smoking cessation was reported to be the major adverse effect worth considering due to the existing inverse relationship between smoking and BMI.[4] The meta-regression indicated that the average BMI of NAFLD participants was positively associated with the NAFLD prevalence in former smokers. More importantly, the NAFLD prevalence of former smokers in the lower BMI (≤30) group was not different from the higher BMI (>30) group (p=0.20). Another study also reported that the NAFLD prevalence remained high (OR=1.76, 95% CI: 1.35 to 2.29, p<0.001) in people without BMI gain (defined as ±1.0 change in BMI) after smoking cessation, even after adjustment for age, sex, income, BMI, hypertension, diabetes mellitus, dyslipidaemia, physical activity and Charlson comorbidity index.[23] These findings indicated that the higher NAFLD prevalence among former smokers was not only due to weight gain after smoking cessation. Since the heterogeneity between studies cannot be completely explained by the gain in BMI, the mechanism behind the NAFLD onset associated with smoking cessation other than weight gain should be studied further in the future.

### The definition and duration of smoking cessation

Smoking status, especially smoking cessation was self-reported in most of the studies included. Thus, the lifetime smoking index was hard to assess among former smokers because of inevitable recall bias. Our result was different from a previous study, that is, Jiang *et al* found that those who quit smoking fewer than 10 years ago had a risk of NAFLD similar to current smokers, while those who quit smoking for more than 20 years had a lower risk of NAFLD.[9] However, we cannot stratify the included studies by the duration of smoking cessation, since studies pooled in our results did not report the time when participants quit smoking. Moreover, objective biochemical tests like urinary cotinine level are unreliable for identifying former smokers because these marks of former smokers are not significantly higher than those of never-smokers.[24]

### Sex difference

Both males and females have the risk of NAFLD after smoking cessation. Our analysis indicated that the risk of NAFLD remained in women after smoking cessation. However, this conclusion may be unstable because few studies performed subgroup analyses by sex, especially for women, which may be because relatively few women are smokers. Thus, the proportion ceasing smoking would be even less.

This study demonstrated that NAFLD prevalence in former smokers was not lower than that in current smokers, consistent with several previous studies.[6 8 25] A cohort study involving 1421 Japanese based on routine health examination also revealed that after adjusting for age, sex, weight loss, hypertension, dyslipidaemia, diabetes mellitus and lifestyle changes, smoking cessation became an independent risk factor for NAFLD (adjusted OR=2.86, 95% CI: 1.24 to 6.62).[8] Despite the absence of direct conclusions, a Mendelian randomisation study[25] reported a positive relationship between the lifetime smoking index and NAFLD (OR=1.59, 95% CI: 1.31 to 1.93 per SD-increase). This would align with our findings, because people who quit smoking may still have a high lifetime smoking index if they were heavy smokers in their early life. However, this systematic review and meta-analysis was based on cross-sectional studies, which cannot conclude the causal relationships between smoking cessation and NAFLD onset. Although studies included covered most regions, data from Africa and Oceania were absent from this study.

### Conclusion

Pooling 28 studies and 4 465 862 participants ranging from 1975 to 2018, our analysis found that NAFLD

prevalence in former smokers was not lower than that in current smokers, indicating that smoking cessation was not a protective factor against NAFLD since the result remained after adjustment for country/region, diagnostic methods, sex, age and BMI. The RR of the overall NAFLD prevalence in former smokers was 1.13 (95% CI: 1.08 to 1.19), with a prediction interval of 0.92–1.39. This result may be partially related to increased BMI after smoking cessation and age. The heterogeneity of the result mostly came from the differences in country/region and NAFLD diagnosis methods. Although under no circumstance can this result become a discouragement of smoking cessation since the benefits of smoking cessation far outweigh the adverse effects,[4] attention should still be paid to the potential NAFLD onset among those who quit smoking. Moreover, weight management and NAFLD onset surveillance are particularly required during the process of smoking cessation.

**Contributors** All authors meet ICMJE criteria for authorship. SZ and ZL performed searches, screened the studies, extracted the data and performed the data analysis. QY, ZH, WZ, YD and GJ contributed substantially to the writing and revising of the paper. GJ and YD supervised the research and acted as guarantor. All authors have read and approved the final manuscript. SZ and ZL have contributed equally to this work. GJ and YD are co-corresponding authors.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not required.

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**Data availability statement** Data are available upon reasonable request.



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