



# Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis

Alessandro Mantovani,<sup>1</sup>  
Christopher D. Byrne,<sup>2,3</sup> Enzo Bonora,<sup>1</sup>  
and Giovanni Targher<sup>1</sup>

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## OBJECTIVE

Several studies have explored the impact of nonalcoholic fatty liver disease (NAFLD) on risk of incident type 2 diabetes. However, the extent to which NAFLD may confer risk of incident diabetes remains uncertain. We performed a meta-analysis of relevant studies to quantify the magnitude of the association between NAFLD and risk of incident diabetes.

## RESEARCH DESIGN AND METHODS

We collected data using PubMed, Scopus, and Web of Science from January 2000 to July 2017. We included only large ( $n \geq 500$ ) observational studies with a follow-up duration of at least 1 year in which NAFLD was diagnosed on imaging methods. Eligible studies were selected according to predefined keywords and clinical outcomes. Data from selected studies were extracted, and meta-analysis was performed using random-effects modeling.

## RESULTS

A total of 19 observational studies with 296,439 individuals (30.1% with NAFLD) and nearly 16,000 cases of incident diabetes over a median of 5 years were included in the final analysis. Patients with NAFLD had a greater risk of incident diabetes than those without NAFLD (random-effects hazard ratio [HR] 2.22, 95% CI 1.84–2.60;  $I^2 = 79.2\%$ ). Patients with more “severe” NAFLD were also more likely to develop incident diabetes; this risk increased across the ultrasonographic scores of steatosis ( $n = 3$  studies), but it appeared to be even greater among NAFLD patients with advanced high NAFLD fibrosis score ( $n = 1$  study; random-effects HR 4.74, 95% CI 3.54–5.94). Sensitivity analyses did not alter these findings. Funnel plot and Egger test did not reveal significant publication bias. Study limitations included high heterogeneity, varying degrees of confounder adjustment across individual studies, and lack of studies using liver biopsy.

## CONCLUSIONS

NAFLD is significantly associated with a twofold increased risk of incident diabetes. However, the observational design of the eligible studies does not allow for proving causality.

Nonalcoholic fatty liver disease (NAFLD) has become the most common liver disease in high-income countries (affecting up to one-third of adults in Europe and the U.S.), and its prevalence is expected to rise further in the near future (1,2).

NAFLD has been traditionally considered to be the simple “hepatic manifestation” of the metabolic syndrome (2,3). Moreover, it is also well known that patients with type 2

<sup>1</sup>Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

<sup>2</sup>Nutrition and Metabolism, Faculty of Medicine, University of Southampton, Southampton, U.K.

<sup>3</sup>Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton, U.K.

Corresponding author: Giovanni Targher, [giovanni.targher@univr.it](mailto:giovanni.targher@univr.it).

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diabetes have a high prevalence of NAFLD (up to 70–75%) and that these patients are also at higher risk of developing non-alcoholic steatohepatitis (NASH) and have a twofold to fourfold higher risk of developing serious liver-related complications (cirrhosis, liver failure, and hepatocellular carcinoma) (4–6).

However, it is now becoming increasingly clear that the link between NAFLD and type 2 diabetes is more complex than previously believed (7–9). NAFLD and type 2 diabetes share multiple cardiometabolic risk factors and pathophysiological (proinflammatory and profibrotic) pathways. In addition, increasing epidemiological evidence suggests that there is a bidirectional relationship between NAFLD and type 2 diabetes and that NAFLD may precede and/or promote the development of type 2 diabetes (3,4,7–9).

To our knowledge, there are only two previously published meta-analyses that have shown that NAFLD is associated with an increased risk of incident diabetes (10,11). However, both of these meta-analyses (published in 2011 and 2016, respectively) also included a large number of observational studies in which the diagnosis of NAFLD was based on abnormal serum liver enzyme levels, which are thought to be only surrogate markers of NAFLD (12). Currently, there is intense debate about the prognostic role of NAFLD per se on the long-term risk of incident diabetes. As will be discussed in detail below, over the past year, numerous large observational studies have been published in which the diagnosis of NAFLD was based on ultrasonography or computed tomography, which are the most widely used noninvasive methodologies to diagnose NAFLD in clinical practice (1–3,12).

We herein report the results of a comprehensive systematic review and meta-analysis of observational cohort studies that has investigated the association between NAFLD (as detected by ultrasonography or other imaging methods) and the risk of incident diabetes. Our aim was to gauge precisely the nature and magnitude of the association between NAFLD and risk of incident diabetes. We have also investigated whether the severity of NAFLD (in studies using either ultrasonographic scoring systems or noninvasive fibrosis markers) is associated with an even greater risk of incident diabetes. Clarification of the magnitude of risk of incident diabetes associated with the different stages of liver disease

within the spectrum of NAFLD may have relevant clinical implications for the diagnosis, prevention, and treatment of type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Registration of Review Protocol

The protocol for this systematic review was registered in advance with PROSPERO (international prospective register of systematic reviews, no. CRD42017072305).

### Data Sources and Searches

Studies were included if they were observational cohort studies that reported the incidence rates of type 2 diabetes in adult individuals ( $>18$  years old) with NAFLD as compared with those without NAFLD. Study participants were of either sex with no restrictions in terms of ethnicity and comorbidities. We included only large ( $n \geq 500$ ) observational studies with a follow-up of at least 1 year in which the diagnosis of NAFLD was based on either imaging or histology in the absence of competing causes of hepatic steatosis. Based on data from the eligible studies, “severe” NAFLD was defined either by presence of increasing ultrasonographic steatosis scores or by high NAFLD fibrosis score (NFS), which is a reliable noninvasive marker of advanced NAFLD fibrosis (12). In these eligible studies, the diagnosis of incident diabetes was based on a self-reported history of disease or use of hypoglycemic drugs, and in most cases, it was also based on a fasting plasma glucose level  $\geq 7.0$  mmol/L or an HbA<sub>1c</sub> level  $\geq 6.5\%$  ( $\geq 48$  mmol/mol).

Exclusion criteria of the meta-analysis were as follows: 1) reviews, editorials, abstracts, case reports, practice guidelines, and cross-sectional studies; 2) studies that used only serum liver enzyme levels, fatty liver index, or other surrogate markers to diagnose NAFLD; 3) studies with a sample size of  $<500$  individuals or with a follow-up duration  $<1$  year; 4) studies conducted in the pediatric population ( $<18$  years old); and 5) studies that did not report any hazard ratio (HR) and 95% CI for the outcome of interest (incident diabetes).

Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Additionally, because included studies were observational in design, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines

for the meta-analysis of observational studies.

### Data Extraction and Quality Assessment

Relevant studies were identified by systematically searching PubMed, Scopus, and Web of Science from 1 January 1990 to 15 July 2017 (date last searched) using the free text terms “fatty liver” (OR “NAFLD” OR “nonalcoholic fatty liver disease” OR “nonalcoholic steatohepatitis”) AND “diabetes risk” OR “diabetes incidence” OR “incident diabetes.” No language restriction was applied. Reference lists of relevant articles and previous review articles were hand searched for other relevant studies. Two investigators (A.M. and G.T.) independently examined all titles and abstracts and obtained full texts of potentially relevant articles. Working independently and in duplicate, we read the articles and determined whether they met inclusion criteria. Discrepancies were resolved by consensus, referring back to the original article, in consultation with a third author. For all studies, we extracted information on study design, study size, source of data, population characteristics, duration of follow-up, outcome of interest, matching, and confounding factors. Additionally, in the case of multiple publications, we included the most up-to-date or comprehensive information.

Two authors (A.M. and G.T.) assessed the risk of bias independently. Since all the included studies were nonrandomized and had a cohort design, the Newcastle-Ottawa Scale (NOS) was used to judge study quality, as recommended by the Cochrane Collaboration (13). This scale uses a star system (with a maximum of nine stars) to evaluate a study in three domains: selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. We judged studies that received a score of nine stars to be at low risk of bias, studies that scored seven or eight stars to be at medium risk, and those that scored six or less to be at high risk.

### Data Synthesis and Analysis

The outcome measure of this meta-analysis was the occurrence of incident diabetes among individuals with NAFLD compared with incidence of diabetes among those without NAFLD. When possible, we pooled adjusted HRs (or odds ratios [ORs]), with their 95% CIs. In the case of studies reporting HRs with varying degrees of adjustment,

we always used the fully adjusted HR estimate. Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. Statistical heterogeneity was assessed by the  $I^2$  statistic, which provides an estimate of the percentage of variability across studies that is due to heterogeneity rather than chance alone. According to Higgins and Thompson (14), a rough guide to interpretation is as follows:  $I^2$  values of  $\sim 25\%$  represent low heterogeneity;  $\sim 50\%$  represent medium heterogeneity; and  $\sim 75\%$  represent high heterogeneity.

The results of the eligible studies were pooled, and an overall estimate of effect size (ES) was calculated using a random-effects model, as this methodology takes into account any differences between studies even if there is no statistically significant heterogeneity (15). Publication bias was evaluated using the funnel plot and Egger regression test (16).

Given the expected heterogeneity of the eligible studies, sensitivity analyses were also carried out to relate the primary outcome (i.e., incident diabetes) with the individual study design characteristics. In particular, based on data from the eligible studies, the prognostic impact of NAFLD on risk of incident diabetes was assessed by stratifying the studies according to the duration of follow-up, the study country, the study design, the "severity" of NAFLD (based on ultrasonographic scoring systems or the NFS), or whether the studies had eight or nine stars on the NOS (i.e., the "high-quality" studies) and whether the studies had full adjustment for covariates (i.e., those studies adjusting at least for age, sex, BMI [or waist circumference], family history of diabetes, fasting glucose levels [or impaired fasting glycemia], lipids, hypertension [or blood pressure values], smoking, and physical activity). Additionally, we tested for possibly excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies at a time. All statistical tests were two sided and used a significance level of  $P < 0.05$ . We used STATA 14.2 (StataCorp, College Station, TX) for all statistical analyses.

## RESULTS

### Characteristics of Included Studies

Based on the titles and abstracts of 2,072 citations, we identified 36 potentially relevant studies. Of these, we excluded

17 studies for the reasons specified in the flow diagram (Supplementary Fig. 1). Thus, 19 unique observational cohort studies were eligible for inclusion in the meta-analysis and were assessed for quality.

As summarized in Table 1, all the eligible studies had an observational retrospective or prospective design (17–35). The eligible studies recruited participants from approximately general populations in which NAFLD was diagnosed by imaging methods (mainly ultrasonography) and incident diabetes was diagnosed by biochemistry (fasting glucose levels or HbA<sub>1c</sub>), clinical history, or drug treatment. No studies with biopsy-proven NAFLD were available for the analysis.

Overall, in the 19 observational cohort studies included in the meta-analysis, there were 296,439 adult individuals (30.1% with NAFLD;  $n = 89,123$ ) with 15,751 cases of incident diabetes over a median follow-up period of 5 years (interquartile range 4.6–9.1). Most of these studies were carried out in Asia (China, Taiwan, South Korea, Sri Lanka, and Japan); two community-based studies were carried out in the U.S. Most of these studies included middle-aged subjects predominantly of male sex. Of the 19 included studies, 10 studies received eight stars at the NOS, 7 studies received six or seven stars, and 2 studies received fewer than six stars, indicating an overall medium risk of bias (Supplementary Table 1).

### NAFLD and Risk of Incident Diabetes

The distribution of studies by estimate of the association between NAFLD and risk of incident diabetes is plotted in Fig. 1. Sixteen studies provided data suitable for the pooled primary analysis ( $n = 214,805$  with 10,356 cases of incident diabetes). We excluded three studies from this primary analysis because the authors did not provide any HR for incident diabetes among individuals with NAFLD pooled together (21,24,32); these three studies were used in a secondary analysis for examining the association between NAFLD severity and diabetes risk (see below).

NAFLD was significantly associated with an increased risk of incident diabetes (random-effects HR 2.22, 95% CI 1.84–2.60;  $I^2 = 79.2\%$ ). Notably, since we always used the fully adjusted HR estimates for each eligible study (as specified in Table 1), this random-effects HR was independent of a relatively large number of

common risk factors and potential confounders. As also shown in Fig. 1, when the comparison was stratified by the study country, the association of NAFLD with risk of incident diabetes was significant in all study countries, but it appeared to be stronger in Japan, China, and Taiwan than in the U.S. and in other Asian countries (South Korea and Sri Lanka).

As shown in Fig. 2, when the comparison was stratified by the length of follow-up period, the association of NAFLD with the risk of incident diabetes appeared to be stronger in those studies with more than 5 years of follow-up ( $n = 16$  studies; random-effects HR 2.60, 95% CI 1.92–3.29;  $I^2 = 74.6\%$ ).

As shown in Supplementary Fig. 2, when the comparison was stratified by the study design, the association between NAFLD and the risk of incident diabetes was consistent in prospective studies ( $n = 3$  studies; random-effects HR 2.25, 95% CI 1.93–2.58;  $I^2 = 0\%$ ) and in retrospective studies ( $n = 13$  studies; random-effects HR 2.26, 95% CI 1.80–2.72;  $I^2 = 81.0\%$ ).

Limiting the analysis to "high-quality" studies and to studies with adjustment for multiple covariates provided overall estimates consistent with the pooled primary analysis ( $n = 10$  studies; random-effects HR 1.85, 95% CI 1.47–2.22;  $I^2 = 68.3\%$ ). Finally, eliminating each of the included studies from the analysis had no effect on the overall risk of incident diabetes (data not shown).

As shown in Supplementary Fig. 3, the Egger regression test did not show statistically significant asymmetry of the funnel plot ( $P = 0.31$ ), thus suggesting that publication bias was unlikely.

### Severe NAFLD and Risk of Incident Diabetes

Four cohort studies reported data on patients with "severe" NAFLD, defined either by ultrasonographic severity of steatosis or by high NFS. The distribution of studies by estimate of the association between severe NAFLD and risk of incident diabetes is plotted in Fig. 3. Compared with the non-NAFLD group, the presence of more "severe" NAFLD was significantly associated with an increased risk of incident diabetes ( $n = 4$  studies; random-effects HR 2.63, 95% CI 1.57–3.70;  $I^2 = 82.4\%$ ). This risk increased across the ultrasonographic scores of hepatic steatosis ( $n = 3$  studies; random-effects HR 2.15, 95% CI 1.72–2.58;

**Table 1—Principal observational (retrospective or prospective) cohort studies of the association between NAFLD (detected by imaging techniques) and the risk of incident type 2 diabetes (ordered by publication year)**

Authors, year (ref.)	Study design; sample size and population; follow-up; and NAFLD diagnostic tool	Diagnosis of incident diabetes (when available)	Number incident cases of diabetes; % in non-NAFLD vs. NAFLD cases	Adjustments considered	Main findings	NOS
Okamoto et al., 2003 (17)	Retrospective cohort study; $n = 840$ (14.3% with NAFLD) Japanese subjects without diabetes; 10 years; liver ultrasonography	Fasting glucose $>6.1$ mmol/L or $HbA_{1c} \geq 6.5\%$	$n = 82$ incident cases; 7.6% vs. 22.5%	Age, sex, BMI, family history of diabetes, fasting glucose, $HbA_{1c}$ , alcohol intake, frequency of check-ups, changes of BMI during follow-up	NAFLD was associated with incident diabetes in univariate analysis (OR 2.62, 95% CI 1.6–4.3). This association disappeared after adjusting for potential confounding factors (aOR 1.83, 95% CI 0.9–3.5)	6
Shibata et al., 2007 (18)	Retrospective cohort study with a nested case-control analysis; $n = 3,189$ (33.6% with NAFLD) male Japanese workers with normal glucose tolerance without known chronic liver diseases; 4 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L or 2-h glucose $\geq 11.1$ mmol/L on 75-g OGTT	$n = 109$ incident cases; 1.8% vs. 8.1%	Age and BMI (in the whole-cohort analysis), age, BMI, smoking history, blood pressure, physical activity, follow-up duration, metabolic syndrome (in the nested case-control analysis)	NAFLD was independently associated with incident diabetes both in the whole cohort (aHR 5.50, 95% CI 3.6–8.5) and in the nested case-control analysis (aHR 4.60, 95% CI 3.0–6.9)	4
Kim et al., 2008 (19)	Retrospective cohort study; $n = 5,372$ (33.3% with NAFLD) South Korean subjects without diabetes without known chronic liver diseases; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, clinical history, or drug treatment	$n = 234$ incident cases; 2.3% vs. 8.5%	Age, sex, BMI, family history of diabetes, smoking, fasting glucose, HDL cholesterol, triglycerides, serum ALT	NAFLD was independently associated with incident diabetes (aHR 1.51, 95% CI 1.04–2.2). Moderate/severe NAFLD had higher HRs vs. mild NAFLD. Exclusion of drinkers did not attenuate this association	8
Bae et al., 2011 (20)	Retrospective cohort study; $n = 7,849$ (29.2% with NAFLD) South Korean subjects without diabetes; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $HbA_{1c} \geq 6.5\%$ , clinical history, or drug treatment	$n = 435$ incident cases; 3.7% vs. 9.9%	Age, sex, BMI, triglycerides, HDL cholesterol, systolic blood pressure, smoking, physical activity, alcohol intake, IFG status	NAFLD was independently associated with incident diabetes (aHR 1.33, 95% CI 1.1–1.7). This association was much stronger in pre-existing IFG	8
Sung et al., 2012 (22)	Retrospective cohort study; $n = 12,853$ (27.6% with NAFLD) South Korean subjects without diabetes; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, clinical history, or drug treatment	$n = 223$ incident cases; 0.8% vs. 4.3%	Age, sex, BMI, educational status, smoking, physical activity, alcohol intake, HOMA-IR, serum triglycerides, serum ALT	The clustering of increased HOMA-IR, overweight/obesity, and NAFLD markedly increases the odds of developing diabetes, with effects independent of each other and of confounding factors. NAFLD was associated with incident diabetes (aOR 2.42, 95% CI 1.7–3.4)	7
Park et al., 2013 (21)	Prospective cohort study (health check-up); $n = 25,232$ (35% with NAFLD) South Korean men without diabetes without known chronic liver diseases; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $HbA_{1c} \geq 6.5\%$ , clinical history	$n = 2,108$ incident cases; 7% in no-steatosis vs. 9.8% in mild steatosis vs. 17.8% in moderate-severe steatosis	Age, waist circumference, HDL cholesterol, triglycerides, systolic blood pressure, C-reactive protein, HOMA-IR, serum creatinine, family history of diabetes, physical activity, metabolic syndrome	NAFLD was independently associated with incident diabetes; the HRs were increased in mild steatosis (1.09, 95% CI 0.8–1.5) and in moderate/severe steatosis (1.73, 95% CI 1.0–3.0) vs. no-steatosis	8
Kasturiratne et al., 2013 (23)	Retrospective cohort study; $n = 2,276$ (40.7% with NAFLD) Sri Lankan individuals without diabetes without known chronic liver diseases; 3 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, clinical history, or drug treatment	$n = 242$ incident cases; 10.5% vs. 19.7%	Age, sex, family history of diabetes, BMI, waist circumference, hypertension, serum ALT, dyslipidemia, IFG status	NAFLD was independently associated with incident diabetes (aHR 1.64, 95% CI 1.2–2.2). NAFLD was the only independent predictor of incident diabetes among those with IFG at baseline	5

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Table 1—Continued

Authors, year (ref.)	Study design; sample size and population; follow-up; and NAFLD diagnostic tool	Diagnosis of incident diabetes	Number incident cases of diabetes; % in non-NAFLD vs. NAFLD cases (when available)	Adjustments considered	Main findings	NOS
Chang et al., 2013 (24)	Retrospective cohort study; $n = 38,291$ (30.4% with NAFLD) South Korean subjects without diabetes without known chronic liver diseases; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $n = 2,025$ incident cases; HbA <sub>1c</sub> $\geq 6.5\%$ , or drug treatment	$n = 2,025$ incident cases; 3.5% in no-NAFLD vs. 7.4% in NAFLD with low NFS vs. 15.3% in NAFLD with intermediate or high NFS	Age, sex, smoking, alcohol intake, physical activity, family history of diabetes, total cholesterol, triglycerides, HDL cholesterol, HOMA-IR, C-reactive protein	The aHRs for incident diabetes in NAFLD with low NFS and NAFLD with intermediate or high NFS vs. no NAFLD were 2.01, 95% CI 1.8–2.2, and 4.74, 95% CI 3.7–6.1, respectively. This association remained significant in subjects with fasting glucose levels $<100$ mg/dL or with HbA <sub>1c</sub> $<5.8\%$	8
Choi et al., 2013 (25)	Retrospective cohort study; $n = 7,849$ (29% with NAFLD) South Korean without diabetes subjects without known chronic liver diseases; 4 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $n = 435$ incident cases; HbA <sub>1c</sub> $\geq 6.5\%$ , or drug treatment	$n = 435$ incident cases; 3.5% in controls vs. 4.6% in the increased ALT vs. 7.3% in the steatosis vs. 11.8% in the combined abnormality group	Age, sex, BMI, systolic blood pressure, triglycerides, HDL cholesterol, IFG status, physical activity, smoking, alcohol intake	The HRs and 95% CI of incident diabetes progressively increased across the elevated ALT, the hepatic steatosis, and the combined abnormality groups. Subjects in the combined abnormality group had the highest risk of incident diabetes (aHR 1.64, 95% CI 1.3–2.1)	8
Yamazaki et al., 2015 (26)	Retrospective cohort study; $n = 3,074$ (23.7% with NAFLD) Japanese subjects without diabetes without known chronic liver diseases; 11.3 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $n = 189$ incident cases; HbA <sub>1c</sub> $\geq 6.5\%$ , clinical history, or drug treatment	$n = 189$ incident cases; 3.1% vs. 16.1%	Age, sex, family history of diabetes, BMI, IFG status, dyslipidemia, hypertension, physical activity	NAFLD was independently associated with incident diabetes (aOR 2.37, 95% CI 1.6–3.5). NAFLD improvement was associated with a reduction of incident diabetes (aOR 0.27, 95% CI 0.1–0.6)	8
Ming et al., 2015 (27)	Retrospective cohort study; $n = 508$ (19.1% with NAFLD) Chinese subjects without diabetes without known chronic liver diseases; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $n = 20$ incident cases; 2-h glucose $\geq 11.1$ mmol/L on 75-g OGTT, or drug treatment	$n = 20$ incident cases; 2.4% vs. 10.3%	Age, sex, educational level, smoking, alcohol intake, physical activity, family history of diabetes, BMI, blood pressure, fasting glucose, 2-h glucose, triglycerides, HDL cholesterol	NAFLD was independently associated with incident diabetes (aHR 4.46, 95% CI 1.9–10.7) but not with incident prediabetes (aHR 1.64, 95% CI 0.97–2.8)	6
Li et al., 2015 (28)	Retrospective cohort study; $n = 4,736$ (29.8% with NAFLD) Chinese subjects without diabetes without known chronic liver diseases; 4 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $n = 380$ incident cases; clinical history, or drug treatment	$n = 380$ incident cases; 4.1% vs. 17.4%	Age, sex, blood pressure, lipids, serum ALT, uric acid, creatinine	NAFLD was independently associated with incident diabetes (aHR 3.37, 95% CI 2.4–4.3)	7
Shah et al., 2015 (29)	Prospective cohort study; $n = 3,153$ (24.9% with NAFLD) U.S. individuals without diabetes from the Multi-Ethnic Study of Atherosclerosis without known chronic liver diseases; 9.1 years; liver computed tomography	Fasting glucose $\geq 7.0$ mmol/L, $n = 216$ incident cases; clinical history, or drug treatment	$n = 216$ incident cases	Age, sex, race, family history of diabetes, BMI, waist circumference, systolic blood pressure, triglycerides, HDL cholesterol, fasting glucose, C-reactive protein, exercise, statin use	NAFLD (defined as first quartile of hepatic attenuation on computed tomography) was independently associated with incident diabetes (aHR 2.06, 95% CI 1.5–2.8; $P < 0.001$ )	8

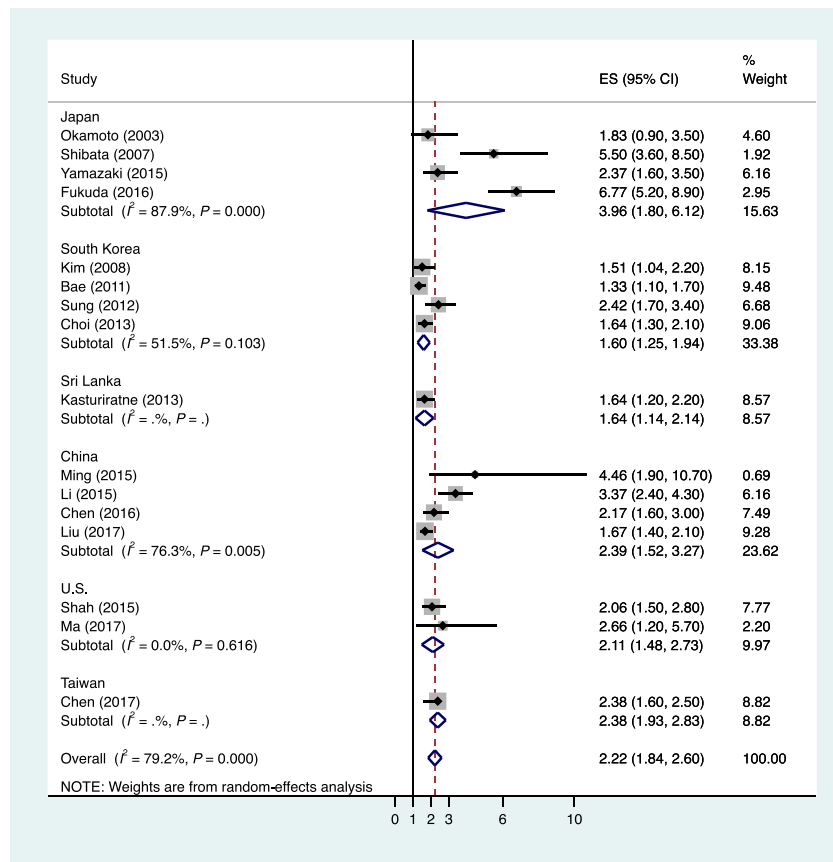
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Table 1—Continued

Authors, year (ref.)	Study design; sample size and population; follow-up; and NAFLD diagnostic tool	Diagnosis of incident diabetes	Number incident cases of diabetes; % in non-NAFLD vs. NAFLD cases (when available)	Adjustments considered	Main findings	NOS
Fukuda et al., 2016 (30)	Retrospective cohort study; $n = 4,629$ (38.4% with NAFLD) Japanese subjects without diabetes without known chronic liver diseases; 12.8 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $HbA_{1c} \geq 6.5\%$ , or drug treatment	$n = 351$ incident cases; 3.2% in nonoverweight, no-NAFLD vs. 14.4% in nonoverweight, NAFLD vs. 8.0% in overweight, no-NAFLD vs. 26.4% in overweight, NAFLD	Age, sex, family history of diabetes, alcohol intake, smoking, regular exercise, $HbA_{1c}$	aHRs for incident diabetes vs. nonoverweight without NAFLD group were 3.59, 95% CI 2.1–5.8, in the nonoverweight with NAFLD group, 1.99, 95% CI 1.5–2.7, in the overweight without NAFLD group, and 6.77, 95% CI 5.2–8.9, in the overweight with NAFLD group, respectively	7
Chen et al., 2016 (31)	Prospective cohort study; $n = 6,542$ (3.2% with NAFLD) Chinese subjects without diabetes without known chronic liver diseases; 6 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, $HbA_{1c} \geq 6.5\%$ , or drug treatment	$n = 368$ incident cases	Age, BMI, triglycerides, fasting glucose, IFG status	NAFLD was independently associated with incident diabetes (aHR 2.17, 95% CI 1.6–3.0)	7
Li et al., 2017 (32)	Prospective cohort study; $n = 18,111$ (31.8% with NAFLD) Chinese subjects without diabetes without known chronic liver diseases; 4.6 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, clinical history, or drug treatment	$n = 1,262$ incident cases; 4.6% in no-NAFLD vs. 10.6% in mild NAFLD vs. 18.1% in moderate-severe NAFLD	Age, sex, BMI, waist circumference, alcohol intake, smoking, exercise, family history of diabetes, fasting glucose, triglycerides, total cholesterol	aHRs for incident diabetes vs. those without NAFLD group were 1.88, 95% CI 1.6–2.2, in the mild NAFLD group and 2.34, 95% CI 1.9–3.0, in the moderate-severe NAFLD group, respectively	8
Ma et al., 2017 (33)	Retrospective cohort study; $n = 1,051$ (17.8% with NAFLD) U.S. individuals without diabetes without known chronic liver diseases; 6.2 years; liver computed tomography	Fasting glucose $\geq 7.0$ mmol/L, clinical history, or drug treatment	$n = 64$ incident cases	Age, sex, smoking, exercise, alcohol intake, fasting glucose, systolic blood pressure, BMI, visceral adipose tissue, and changes in BMI, visceral adipose tissue, and liver fat during follow-up	NAFLD was independently associated with incident diabetes (aOR 2.66, 95% CI 1.2–5.7)	8
Chen et al., 2017 (34)	Prospective cohort study; $n = 132,377$ (32% with NAFLD) Taiwanese subjects without diabetes without known chronic liver diseases; 18 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, clinical history, or drug treatment	$n = 6,555$ incident cases	Age, sex, BMI, hypertension, family history of diabetes, smoking, alcohol intake, exercise, triglycerides, HDL cholesterol, total cholesterol, serum AST, ALT, GGT, and ALP levels	NAFLD was independently associated with incident diabetes (aHR 2.38, 95% CI 1.6–2.5, for the whole sample; aHR 2.08, 95% CI 1.9–2.2, for men and aHR 2.65, 95% CI 1.4–2.9, for women)	8
Liu et al., 2017 (35)	Retrospective cohort study; $n = 18,507$ (18.8% with NAFLD) Chinese elderly men without diabetes without known chronic liver diseases; 5 years; liver ultrasonography	Fasting glucose $\geq 7.0$ mmol/L, 2-h glucose $\geq 11.1$ mmol/L on 75-g OGTT, clinical history, or drug treatment	$n = 453$ incident cases; 2.1% vs. 3.7%	Age, BMI, smoking, marital status, alcohol intake, hypertension, dyslipidemia	NAFLD was independently associated with incident diabetes (aHR 1.67, 95% CI 1.4–2.1)	7

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aHR, adjusted HR; aOR, adjusted OR; GGT,  $\gamma$ -glutamyl transferase; HOMA-IR, HOMA of insulin resistance; IFG, impaired fasting glycemia; OGTT, oral glucose tolerance test.





**Figure 1**—Forest plot and pooled estimates of the effect of NAFLD on the risk of incident diabetes in 16 eligible studies, stratified by study country. ES, effect size.

$I^2 = 0\%$ ), but it appeared to be even greater among NAFLD patients with high NFS ( $n = 1$  study; random-effects HR 4.74, 95% CI 3.54–5.94). However, only a single study assessed NAFLD severity by using NFS, and no studies involving non-Asian individuals were available for this analysis, thus limiting the generalizability of the finding.

## CONCLUSIONS

Our meta-analysis provides evidence for a significant association between imaging-diagnosed NAFLD and the long-term risk of incident diabetes. Indeed, this meta-analysis involves a total of 19 unique observational studies with aggregate data on 296,439 adult individuals (30.1% with NAFLD) and nearly 16,000 cases of incident diabetes followed up over a median period of 5 years.

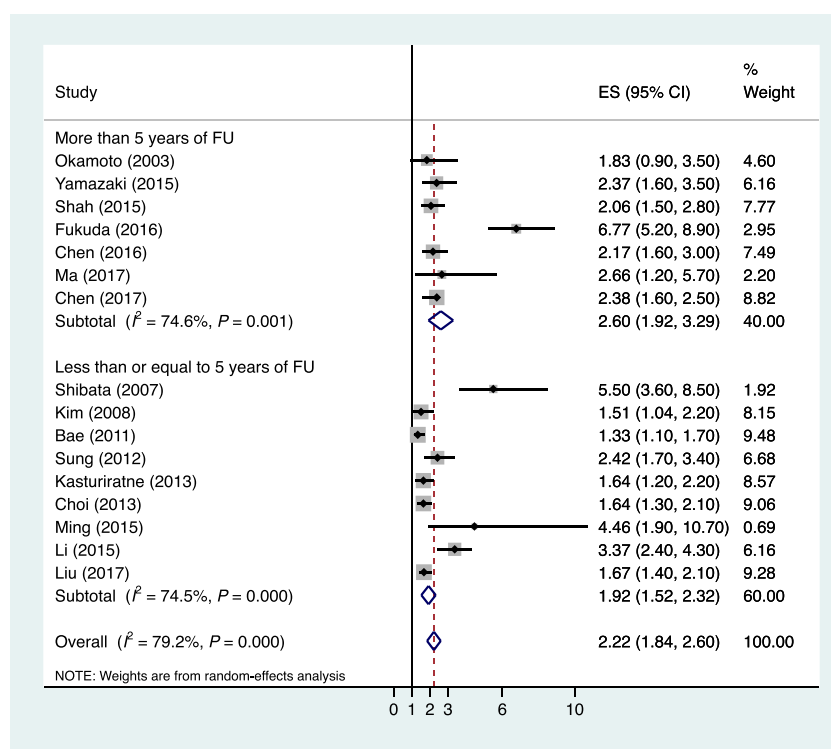
We found that the presence of imaging-diagnosed NAFLD conferred a HR of 2.2 for incident diabetes, a risk that appeared to increase further with greater “severity” of NAFLD (assessed in four observational studies using either the ultrasonographic

severity of steatosis or the NFS) and remained statistically significant in those studies where analysis was fully adjusted for potentially confounding factors ( $n = 10$  studies; random-effects HR 1.85, 95% CI 1.47–2.22;  $I^2 = 68.3\%$ ). In addition, when the analysis was stratified either by follow-up duration or by study country, the association between NAFLD and diabetes risk appeared to be stronger in studies with a follow-up duration longer than 5 years and in studies performed in Japanese and Chinese populations compared with those conducted in the U.S. and in other Asian countries.

Unfortunately, most of the published studies that used liver biopsies to diagnose NAFLD (i.e., the “gold standard” method for diagnosing and staging NAFLD) did not have a control group and cannot, therefore, be included in this meta-analysis. To date, however, very little is known about how long-term NAFLD or its histologic features may affect risk of incident diabetes. A retrospective cohort study of 396 patients

with biopsy-confirmed NAFLD, who did not have diabetes at baseline, reported that a significantly higher proportion of patients with fibrosis stages 3–4 developed incident diabetes than those with fibrosis stages 0–2 (51% vs. 31%) over a mean follow-up of 18.4 years (36). Interestingly, for patients with fibrosis stages 0–2, fat score was also independently associated with incident diabetes (36). The issue of whether the increased diabetes risk is confined to patients with more severe NAFLD or applies to all patients with NAFLD is particularly relevant in view of the disease burden that NAFLD represents and might impact on the health care resources needed to survey and manage these patients adequately. The results of our meta-analysis (based exclusively on studies using ultrasonographic scoring systems or the NFS) suggest that it is more advanced NAFLD that carries a greater diabetes risk. This is also consistent with the conclusion of another comprehensive meta-analysis supporting a link between NAFLD severity and risk of fatal and nonfatal cardiovascular events (37). However, this question remains largely unsolved, and further follow-up studies in larger cohorts of both Asian and non-Asian individuals with biopsy-confirmed NAFLD (with an adequate group of control individuals) are needed in order to definitely establish whether NAFLD severity differentially affects risk of incident diabetes.

This is the largest and most updated meta-analysis aimed at investigating the prognostic role of imaging-diagnosed NAFLD on the long-term risk of incident diabetes. Collectively, our findings confirm and extend (with a sample size at least three times larger) the results of two previous meta-analyses that incorporated studies using both abnormal serum liver enzymes and imaging techniques to diagnose NAFLD (10,11). In the first meta-analysis, Musso et al. (10) in 2011 reported that ultrasound-diagnosed NAFLD (only three studies included) was associated with an increased risk of incident diabetes (random-effects OR 3.51, 95% CI 2.28–5.41;  $I^2 = 70\%$ ). In the second meta-analysis, Ballestri et al. (11) confirmed that NAFLD (defined by ultrasonography; only nine studies included in total) significantly increased the risk of incident diabetes over a follow-up of nearly 5 years (random-effects OR 1.86, 95% CI 1.76–1.95;  $I^2 = 86\%$ ).



**Figure 2**—Forest plot and pooled estimates of the effect of NAFLD on the risk of incident diabetes in 16 eligible studies, stratified by length of follow-up (FU) (based on the median follow-up of the eligible studies). ES, effect size.

Notably, our meta-analysis is the first to show that the association between NAFLD and the risk of incident diabetes is stronger in some ethnic groups (especially in Japanese individuals) and in studies with longer follow-up duration and that the more “severe” forms of NAFLD seem to be associated with an even greater risk of developing diabetes. This latter finding is also indirectly supported by the results of the study of Ma et al. (33) demonstrating that among the Framingham Heart Study participants, baseline hepatic fat content (per SD increase) was independently associated with increased odds of incident diabetes over ~6 years of follow-up.

There is now convincing evidence of biological plausibility that NAFLD may increase risk of incident type 2 diabetes (3,4,7,8). Indeed, NAFLD, especially NASH with varying levels of hepatic fibrosis, exacerbates hepatic insulin resistance and causes the release of multiple proinflammatory mediators and prodiabetogenic hepatokines (e.g., fetuin-A, fetuin-B, fibroblast growth factor 21, retinol binding protein 4, and selenoprotein P) that may promote the development of diabetes (38–40). Among the hepatokines, data about fetuin-A action in mice and in humans

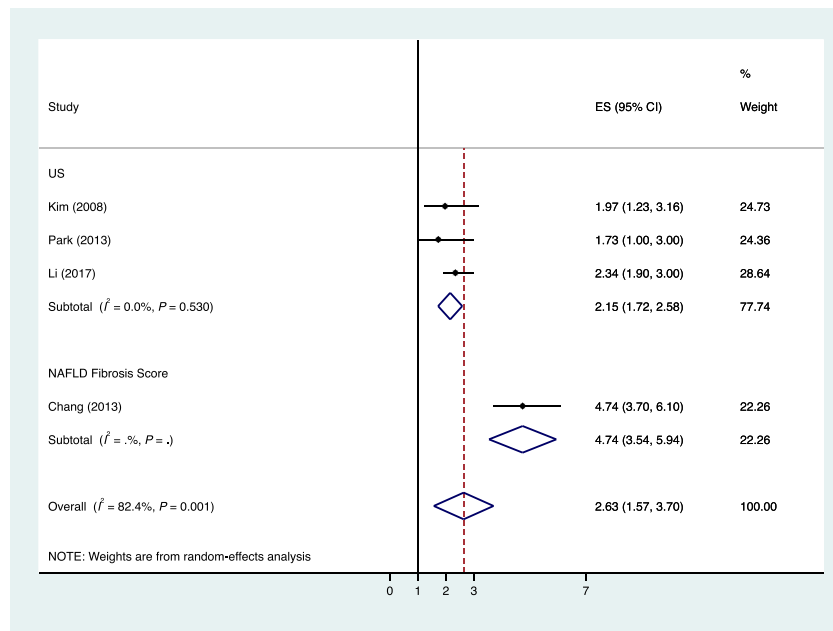
in particular supports a causative relationship of NAFLD with incident diabetes (38,41,42). However, whether improvement or resolution of NAFLD could decrease risk of incident diabetes remains uncertain. Some evidence suggests that the risk of diabetes appears to diminish over time following the resolution or improvement of NAFLD (26,43). However, as these two studies are not randomized controlled trials of NAFLD management, these results should be interpreted cautiously.

Although our meta-analysis of observational studies provides support for the existence of a significant association between NAFLD and increased risk of incident diabetes, it remains to be definitively proven that improving the liver condition in NAFLD decreases risk of developing diabetes. It should also be noted that there may be a dissociation between NAFLD and insulin resistance in humans carrying some genetic variants, such as the patatin-like phospholipase 3 gene (44). Experimental evidence (mainly derived from animal studies) also indicates that specific manipulation of liver fat is insufficient to affect insulin sensitivity/glycemia (45–47). In addition, it is known that there are

ethno-racial differences in liver fat content (as well as in the amount of lipid accumulated in skeletal muscle and abdominal cavity) and risk of diabetes. For example, compared with white individuals, obese black individuals exhibit a lower prevalence of NAFLD but similar type 2 diabetes prevalence (48–50). That said, our data strongly emphasize that there is a real need now to include outcomes such as incident diabetes and changes in HbA<sub>1c</sub> and insulin sensitivity in randomized placebo-controlled trials focused on testing the efficacy of novel therapies for liver disease in NAFLD. Improved understanding of these features and precise phenotyping of NAFLD could help to improve stratification of cardiometabolic risk. This might also have important implications for future strategies in the prevention and treatment of type 2 diabetes and other cardiometabolic diseases in clinical practice (51,52).

Our meta-analysis has some important limitations (strictly inherent to the nature of the included studies) that should be mentioned. Although we used a random-effects model, the interpretation of the results of this meta-analysis requires some caution, given the (expected) high heterogeneity ( $I^2 > 75\%$ ) observed in the overall primary analysis. It is plausible to assume that this high heterogeneity likely reflects differences in the demographic and ethno-racial characteristics of study populations, in the length of follow-up, in the design of the study, and in the severity of NAFLD. We systematically explored and identified all these possible sources of statistical heterogeneity using stratified analyses and sensitivity analyses (as detailed in the RESULTS section). Although we found significant heterogeneity between studies when investigating associations in the overall analysis, it is noteworthy that there was very low heterogeneity between studies, as well as stronger associations between NAFLD and diabetes risk, when we restricted the statistical analyses to studies with only the more “severe” forms of NAFLD on ultrasonography, studies with a prospective design (compared with retrospective ones), or studies performed in the U.S. population. However, we believe that more detailed analyses of the causes of heterogeneity will require collaborative pooling of individual participant data from large prospective studies as these become available over time.





**Figure 3**—Forest plot and pooled estimates of the effect of the severity of NAFLD (defined by ultrasonography [US] or high NFS) on the risk of incident diabetes in four eligible studies. ES, effect size.

Another potential limitation of the meta-analysis (strictly inherent to the observational nature of the included studies) is that information about the temporal changes of some important variables (e.g., medication use and lifestyle changes) that may impact NAFLD and incident diabetes is often missing and that the varying degree of confounder adjustment across the individual studies hampered a systematic assessment of the impact of known risk factors on the outcome of interest. As shown in Table 1, some studies reported incomplete adjustments for established risk factors and potential confounders (e.g., waist circumference or insulin resistance); as such, it was not possible to combine models in studies that adjusted for the same set of potential confounding factors. Another limitation of the meta-analysis was that none of the eligible studies used liver biopsy for the diagnosis of NAFLD. Conversely, most of the eligible studies used ultrasonography, which is the recommended first-line imaging method for detecting NAFLD in clinical practice and enables a reliable and accurate detection of mild-to-moderate hepatic steatosis compared with liver histology. Furthermore, the results regarding the association between the severity of NAFLD and diabetes risk derived from very few studies, and only a single study assessed NAFLD severity by using the NFS.

Additionally, since the diagnosis of diabetes was not always consistent among the included studies, some inaccuracy in the estimated incidence of diabetes and in the identification of diabetes subtypes may not be excluded (although the vast majority of diabetes cases were likely to be type 2). Despite the fact that both fasting plasma glucose and HbA<sub>1c</sub> levels were available for the majority of the eligible studies, the diagnosis of diabetes was based on HbA<sub>1c</sub> or fasting glucose measurements, without further systematic confirmation by a second determination on a separate day; however, this is an intrinsic limitation of all large observational studies, in which the confirmation of diabetes diagnosis, on at least two separate occasions, has been never made. Finally, in none of the published studies, except for the studies by Shibata et al. (18) and Ming et al. (27), was the diagnosis of diabetes based on 2-h postload plasma glucose levels.

Notwithstanding these limitations, the present meta-analysis has several important strengths. As discussed previously, this meta-analysis provides the most comprehensive assessment to date on the independent prognostic impact of NAFLD on the long-term risk of incident diabetes. These results, obtained by analyzing more than 15,000 new cases of incident diabetes among nearly 300,000 individuals (incorporating data from

observational cohort studies that are likely to be an accurate reflection of NAFLD patients commonly seen in routine clinical practice), provide clear evidence that diabetes risk of individuals with NAFLD is significantly higher than that of individuals without NAFLD (with a high level of heterogeneity for the pooled primary analysis and a medium-low quality of the mainly retrospective available studies). Moreover, it is important to underline that we employed standardized risk estimates from all eligible studies to allow a consistent combination of estimates across studies. The large number of incident cases of diabetes provided high statistical power to quantitatively assess the association between NAFLD and diabetes risk. Finally, selective reporting bias of studies was not a concern in our analyses, as our comprehensive search and contact with investigators made it unlikely that any published report was missed and visual inspection of plots and formal tests demonstrated no statistical evidence of publication bias.

Currently, there are no approved pharmacological agents for the treatment of NAFLD. Most interventions evaluated for NAFLD treatment are those commonly used for the treatment of type 2 diabetes and exert a rather indirect effect on the liver through improvements in both insulin sensitivity and insulin action, decreases in free fatty acid levels, and improvements in glucose uptake (4,8,53). These pharmacological interventions have also been to date the most effective treatments for NAFLD, which is perhaps not surprising, considering the high degree of interplay between these two diseases.

In conclusion, this largest and most comprehensive meta-analysis to date showed that imaging-diagnosed NAFLD is associated with an approximate doubling of risk of incident diabetes and that this risk seems to be even greater in presence of more “severe” liver disease (in the few available cohort studies using ultrasonographic scoring systems or noninvasive fibrosis markers). Because no studies with biopsy-proven NAFLD were available for the analysis, the findings of this meta-analysis pave the way for future large, prospective, histologically based studies. It remains uncertain whether NAFLD causally increases diabetes risk or is a marker of other shared risk factors. Further studies are also needed in non-Asian populations, as most of the published studies have

been conducted in Asian populations, where large populations undergo regular health checkups, including liver ultrasonography. Finally, additional studies are also required to establish whether adding NAFLD (or the different components of liver disease in NAFLD) to the currently available algorithms will improve risk prediction for diabetes. Despite the above-mentioned caveats, current clinical guidelines do recommend routine screening for diabetes in patients with NAFLD (53), and therefore there is a need to clarify the magnitude of risk of incident diabetes that is associated with the stages of liver disease in NAFLD.

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