Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults

Myriam Alexander,[1] A Katrina Loomis,[2] Johan van der Lei,[3] Talita Duarte-Salles,[4] Daniel Prieto-Alhambra,[5] David Ansell,[6,7] Alessandro Pasqua,[8] Francesco Lapi,[8] Peter Rijnbeek,[3] Mees Mosseveld,[3] Paul Avillach,[3,9] Peter Egger,[1] Nafeesa N Dhalwani,[10] Stuart Kendrick,[11] Carlos Celis-Morales,[12] Dawn M Waterworth,[13] William Alazawi,[14*] Naveed Sattar[12*]

For numbered affiliations see end of the article.

*Contributed equally

Correspondence to: N Sattar
Naveed.sattar@glasgow.ac.uk
(ORCID 0000-0002-1604-2593)

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ABSTRACT

OBJECTIVE

To estimate the risk of acute myocardial infarction (AMI) or stroke in adults with non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

DESIGN

Matched cohort study.

SETTING

Population based, electronic primary healthcare databases before 31 December 2015 from four European countries: Italy (n=1 542 672), Netherlands (n=2 225 925), Spain (n=5 488 397), and UK (n=12 695 046).

PARTICIPANTS

120 795 adults with a recorded diagnosis of NAFLD or NASH and no other liver diseases, matched at time of NAFLD diagnosis (index date) by age, sex, practice site, and visit, recorded at six months before or after the date of diagnosis, with up to 100 patients without NAFLD or NASH in the same database.

MAIN OUTCOME MEASURES

Primary outcome was incident fatal or non-fatal AMI and ischaemic or unspecified stroke. Hazard ratios were estimated using Cox models and pooled across databases by random effect meta-analyses.

RESULTS

120 795 patients with recorded NAFLD or NASH diagnoses were identified with mean follow-up 2.1-5.5 years. After adjustment for age and smoking the pooled hazard ratio for AMI was 1.17 (95% confidence interval 1.05 to 1.30; 1035 events in participants with NAFLD or NASH, 67 823 in matched controls). In a group with more complete data on risk factors (86 098 NAFLD and 4 664 988 matched controls), the hazard ratio for AMI after adjustment for systolic blood pressure, type 2 diabetes, total cholesterol level, statin use, and hypertension was 1.01 (0.91 to 1.12; 747 events in participants with NAFLD or NASH, 37 462 in matched controls). After adjustment for age and smoking status the pooled hazard ratio for stroke was 1.18 (1.11 to 1.24; 2187 events in participants with NAFLD or NASH, 134 001 in matched controls). In the group with more complete data on risk factors, the hazard ratio for stroke was 1.04 (0.99 to 1.09; 1666 events in participants with NAFLD, 83 882 in matched controls) after further adjustment for type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension.

CONCLUSIONS

The diagnosis of NAFLD in current routine care of 17.7 million patient appears not to be associated with AMI or stroke risk after adjustment for established cardiovascular risk factors. Cardiovascular risk assessment in adults with a diagnosis of NAFLD is important but should be done in the same way as for the general population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Non-alcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome and other risk factors for acute myocardial infarction (AMI) or stroke

NAFLD is associated with increased risk of AMI and stroke and cardiovascular surrogate markers

The association between NAFLD and AMI and stroke after adjustment for established risk factors has yet to be fully established however

WHAT THIS STUDY ADDS

In four large European databases, the adjusted hazard ratios for incident AMI or stroke diagnoses in adults with NAFLD were modest and not significantly greater than those in age, sex, and general practice matched participants without NAFLD

Introduction

For several years, researchers have proposed that, in addition to being a marker of ectopic fat accumulation and diabetes risk (which is unambiguous), non-alcoholic fatty liver disease (NAFLD) might have important associations with cardiovascular outcomes.[1] The incidence of NAFLD has increased alongside that of obesity and diabetes worldwide, however its "impact" on complications from those conditions, including risk of cardiovascular disease, has not yet been established. In some ways this is not surprising because people with NAFLD often have abnormal glucose and lipid levels and are usually overweight or obese. Other mechanisms that could explain a possible association include increased oxidative stress, deranged adipokine profile, and hypercoagulability, which are more likely in people with NAFLD,[2] giving rise to risk of AMI or stroke beyond those of traditional risk factors. Studies have shown an increased prevalence of surrogate markers in people with NAFLD: subclinical atherosclerosis,[3-5] subclinical AMI or stroke (Framingham study),[3] and carotid atherosclerotic plaques.[6 7] The severity of coronary artery disease was also higher in people with NAFLD referred for coronary angiography.[8]

Results from recent meta-analyses indicate that people with NAFLD are at risk of AMI or stroke. For

example, one meta-analysis reported an odds ratio of 2.05 (95% confidence interval 1.81 to 2.31) for incident cardiovascular disease events in people with ultrasound defined NAFLD compared with controls without NAFLD.[9] Similarly, a recent meta-analysis of more than 34 000 participants reported an odds ratio of 1.64 (95% confidence interval 1.26 to 2.13) for combined fatal and non-fatal AMI or stroke events.[10] Heterogeneity in these two meta-analyses was moderate to high and the authors mentioned potential bias from variable and often incomplete adjustment for usual risk factors. Despite this limitation, the findings seem to suggest that people with NAFLD have risk levels for AMI or stroke approaching those for people with type 2 diabetes. Such findings support the suggestion that all people with NAFLD should be treated for prevention of cardiovascular disease.[1]

The degree to which NAFLD contributes to the increased incidence of AMI or stroke is, however, debatable,[11] particularly as most of the studies included in the two recent meta-analyses[9 10] only partially adjusted for known risk factors, such as diabetes and lipid levels, which often coexist with NAFLD. In addition, few previous studies have considered geographical and other socioeconomic sources of heterogeneity. Furthermore, robust assessments of AMI or stroke risk in people with NAFLD compared with the general population are important to establish in routine healthcare in the real world, to help inform doctors about the management of cardiovascular risk in people with a diagnosis of NAFLD in routine clinical care. Such data would also help to determine whether an AMI or stroke risk multiplier should to be introduced for those with NAFLD, as has been done for people with diabetes or rheumatoid arthritis.[12] We therefore undertook a longitudinal analysis of people with a recorded diagnosis of NAFLD in four European primary care databases, as part of the European Medical Information Framework (EMIF) to estimate the incident risk of developing acute myocardial infarction (AMI) and stroke in those cohorts identified in routine practice. When data were available, we sequentially adjusted for known cardiovascular risk factors, and in sensitivity analyses we investigated the associations in people with NAFLD without a subsequent diagnosis of NASH.

Methods

Databases

We included patient data from four primary care databases available through the EMIF network: The Health Improvement Network (THIN, UK), Health Search Database (HSD, Italy), Information System for Research in Primary Care (SIDIAP, Spain), and Integrated Primary Care Information (IPCI, Netherlands).[13-17] The databases are compliant with local data protection laws. During data extraction, each data custodian liaised with the European Medicine Information Framework (EMIF)-Platform (www.emif.eu). Data were then uploaded using a private remote secure server and analysed centrally.

Study design

We adopted a matched cohort design. To ensure comparability between databases we generated code lists for clinical diagnoses (exclusion criteria, exposure, covariates, and events of interest) using a semantic harmonisation process that involved mapping concepts in each terminology (ICD-9 (international classification of diseases, ninth revision) codes for HSD, ICPC Dutch for IPCI, ICD-10 for SIDIAP, and Read codes for THIN) to unified medical language system concepts.[18] In the four databases we identified people with a diagnosis of NAFLD (including non-alcoholic steatohepatitis (NASH)) before 1 January 2016. Owing to differences in coding terminology, recording of NASH diagnoses as distinct from NAFLD diagnoses was only possible in Spain (SIDIAP) and the UK (THIN). In the main analyses in these databases, people with NAFLD and NASH were grouped together, as was also the case in IPCI and HSD owing to the coding (ICPC Dutch codes and ICD-9 do not have distinctive codes for NAFLD and NASH). We carried out sensitivity analyses in SIDIAP and THIN excluding participants with NASH.

Each participant with NAFLD was matched with up to 100 participants without a diagnosis of NAFLD or NASH. Index date was the date of NAFLD diagnosis for each paired set. Matching was done on practice site (as a proxy for socioeconomic deprivation),[19] age at index date within five years either way, sex, and a recorded date for visiting a general practitioner at index date within six months either way.

Participants with NAFLD and their matched controls were included in the analysis if they were aged 18 or more at diagnosis, remained active in the database for at least 12 months from registration and six months before the index date, and had at least six months of follow-up after the index date. We excluded participants with a record of alcohol misuse at any time before diagnosis or a past AMI or stroke event. Supplementary table 1 shows the flow chart of inclusion and exclusion criteria.

Participants were followed-up from index date until the earliest of occurrence of an event, end of study period (31 December 2015), or loss to follow-up owing to exit from the database or death. Events of interest were fatal or non-fatal AMI and ischaemic or unspecified stroke.

Variables

In Europe, primary care doctors store information on clinical diagnoses, prescriptions, lifestyle (smoking behaviours), vital signs, and procedures, and sometimes on socioeconomic information. When a patient is referred to a specialist in secondary care settings, referral letters containing patient's notes and laboratory results are sent back to primary care doctors, for inclusion into the patient's medical records. As such, personal information, lifestyle, and medical history on relevant morbidities could be extracted from the participants' records. We extracted total cholesterol levels and systolic blood pressure for two years before to six months after the index date. If

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participants had a record of being a smoker within five years before the index date or any time after the index date we defined them as a smoker, otherwise a non-smoker. Statin use was coded as yes if participants had a record of a statin prescription in the two years before and within six months after the index date. History of type 2 diabetes and hypertension were defined as a record occurring any time before or at the index date.

Data analysis

Analyses were performed using a two step approach for data synthesis. Firstly, we analysed each of the four databases separately and then we used a random effect meta-analysis to pool the estimates for each of these studies. Matched pairs (participants with NAFLD matched with participants without NAFLD) are described using percentages for categorical variables, means and standard deviations for normally distributed variables, and medians and interquartile ranges for skewed variables. Within each group we estimated incidence rates of AMI and stroke by dividing the number of incident events by the total number of person years at risk, and the corresponding 95% confidence intervals were estimated assuming a Poisson distribution. Hazard ratios for incident AMI or stroke associated with a diagnosis of NAFLD were estimated using Cox proportional hazards models for each study independently. The models were stratified by matching variables and progressively adjusted in multivariable models for age and smoking status, and age, smoking status, type 2 diabetes, statin use, hypertension, systolic blood pressure, and total cholesterol level (in subsets of participants with data available). We then pooled hazard ratios across studies by random effects meta-analysis. The Q statistic was used to test heterogeneity across databases,[20] which has a χ^2 distribution with 2 degrees of freedom on the null hypothesis of no heterogeneity, and the corresponding P value was obtained. We also reported the I^2 statistic, which gives the percentage of variation among studies due to heterogeneity across databases, rather than to variation among individual people within a database.[21] Hazard ratios were estimated by prespecified subgroups according to sex, BMI (obese, ≥30 *v* normal weight), smoking status, age group (<55 years *v* ≥55 years old), hypertension status, and type 2 diabetes status. For this, we added an interaction term to the models between NAFLD diagnosis and subgroup, and we then used random effects meta-analyses to pool hazard ratios for each subgroup across databases. We excluded values that were physiologically implausible: BMI less than 15, laboratory values greater than the mean in the database plus three times the standard deviation, aspartate aminotransferase and alanine aminotransferase levels less than 5 iU/L, and platelet counts less than 5×10^9/L. Missing data were not imputed and analyses were run in the samples of participants with no missing data for all variables in the models.

The data were locally extracted within each centre after quality control checks using a standardised script. They were then centrally analysed using Stata v14 on the secure remote research server of the EMIF Platform.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. However, patients were involved in the setup of the overall European Medical Information Framework consortium, which underpinned this work. No patients were asked to advise on interpretation or writing up of results. The results of the research will be disseminated to patients through the European Medical Information Framework website (emif.eu).

Results

Primary care records for 21 952 040 patients resident in four European countries were accessed: Italy (HSD, n=1 542 672), Netherlands (IPCI, n=2 225 925), Catalonia, Spain (SIDIAP, n=5 488 397), and UK (THIN, n=12 695 046).[13-16] After excluding patients with a history of alcohol misuse, a past AMI or stroke event, less than one year of enrolment, and less than six months of follow-up before and after the index date, 120 795 participants with an incident NAFLD diagnosis (21 627 in HSD, 12 595 in IPCI, 67 109 in SIDIAP, and 19 464 in THIN) were included.

Baseline characteristics

The duration of follow-up before and after the index date, age distribution, and percentage of men were comparable in the NAFLD and non-NAFLD groups in each of the four databases (table 1).[13-16] Average follow-up after the index date was lowest in IPCI (median 2.1 years (interquartile range 1.2-3.4 years) and highest in HSD (5.5 (3.0-8.1) years) in participants with NAFLD. Traditional cardiovascular risk factors were more common in participants with NAFLD compared with matched controls: proportions of current smokers (except for THIN), participants with a history of type 2 diabetes or hypertension, BMI levels, and systolic blood pressure levels were higher in participants with NAFLD compared with matched controls in each of the four databases.

Outcome incidence rates

The total number of person years' follow-up for participants with NAFLD or NASH ranged from 85 361 in THIN to 259 008 in SIDIAP (supplementary table 2). Unadjusted incidence rates of AMI and stroke were higher in participants with NAFLD compared with matched controls and differed across databases: rates of AMI were highest in IPCI (4.36 (95% confidence interval 3.66 to 5.15) and 3.17 (3.11 to 3.24) per 1000 person years in participants with and without NAFLD, respectively); whereas rates of stroke were highest in HSD (7.88 (7.39 to 8.39) and 6.27 (6.22 to 6.32) per 1000 person years, respectively) (supplementary table 2**)**. In participants with NAFLD, the number of incident AMI events ranged from 137 (in IPCI) to 414 (in SIDIAP), and stroke events from 156 (in IPCI) to 962 (in HSD).

To investigate whether these associations were modified by common risk factors for cardiovascular disease, we defined subsets of participants in whom we had data on total cholesterol level and systolic blood pressure, and participants for whom we additionally held data on BMI and HDL cholesterol level. In the former subset, 86 098 participants with NAFLD experienced 747 AMI events and 1666 stroke events during follow-up (supplementary table 3). Participants in the subset with more complete data were more likely to have type 2 diabetes, hypertension, be prescribed statins, and be current smokers compared with the entire NAFLD cohort in each database (supplementary table 4).

Hazard ratios for incident AMI

When adjustments were made for age, sex, and smoking, the hazard ratio for incident AMI in participants with NAFLD ranged from 1.03 (95% confidence interval 0.90 to 1.18) in HSD to 1.31 (1.16 to 1.49) in THIN; the pooled hazard ratio was 1.17 (1.05 to 1.30), I^2=66%, P=0.03 for heterogeneity) (fig 1). When analyses were done in the subset of participants with full data on traditional risk factors for cardiovascular disease, the age, sex, and smoking adjusted hazard ratio for incident AMI was 1.08 (0.96 to 1.23) which, when adjusted for systolic blood pressure, type 2 diabetes, total cholesterol level, statin use, and hypertension attenuated to 1.01 (0.91 to 1.12), I^2=48.4%, P=0.12 for heterogeneity). Excluding participants with NASH did not alter the lack of association between NAFLD and AMI (supplementary fig 1). In subgroup analyses, pooled hazard ratios did not significantly differ according to presence or absence of type 2 diabetes or hypertension, or by smoking status, age group, obesity, and sex (although estimates were slightly higher in women than in men) (supplementary fig 2).

Hazard ratios for incident stroke

For the model minimally adjusted for age, sex, and smoking the pooled hazard ratio for incident stroke was 1.18 (1.11 to 1.24) with low levels of heterogeneity across databases (I^2=29.3% and P=0.24) (fig 2). In the subset with mostly complete data on risk factors, the pooled hazard ratio for stroke was 1.10 (1.04 to 1.15) in the minimally adjusted model, which became attenuated to 1.04 (0.99 to 1.09), I^2=0.0%, P=0.92 for heterogeneity) after adjustment for type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension. Associations between NAFLD and incident stroke were unchanged after excluding participants with NASH (supplementary fig 3). Subgroup analyses did not identify any significant differences, although the hazard ratio was marginally higher for woman than for men (1.15 *v* 1.04) (supplementary fig 4).

Hazard ratios were not materially different in sensitivity analyses including recurrent AMI and stroke events and participants with less than six months of follow-up (supplementary figs 5-7).

Discussion

In this real world primary care record study of 205 046 cardiovascular events in 120 795 adults and 9 647 644

Table 1 | Descriptive characteristics of participants with non-alcoholic fatty liver disease (NAFLD) and matched participants in four European primary care databases

	HSD (Italy)		IPCI (Netherlands)		SIDIAP (Spain)		THIN (UK)	
Characteristics	NAFLD	Matched non- NAFLD	NAFLD	Matched non- NAFLD	NAFLD	Matched non- NAFLD	NAFLD	Matched non- NAFLD
Median (interquartile range) follow-up before index date (years)	7.5 (4.7-10.4)	7.6 (4.8-10.4)	2.5 (1.4-3.9)	2.5 (1.4-3.9)	5.1 (3.1-6.8)	5.1 (3.1-6.8)	13.4 (5.8-22.9)	14.3 (6.6-23.2)
Median (interquartile range) follow-up post index date (years)	5.5 (3.0-8.1)	5.4 (3.0-8.1)	2.1 (1.2-3.4)	2.2 (1.2-3.4)	3.7 (2.0-5.6)	3.7 (2.0-5.7)	3.5 (1.8-6.1)	3.5 (1.8-6.1)
Mean (SD) age (years)	55.6 (14.2)	54.6 (13.5)	56.1 (13.6)	55.6 (13.3)	55.6 (13.3)	54.2 (12.9)	53.3 (13.1)	52.9 (13.2)
Men (%)	57.2	54.9	48.6	48.1	52.5	48.8	51.1	50.4
Current smokers (%)	11.3	9.1	17.2	11.1	17.8	15.4	17.3	18.7
Mean (SD) body mass index	29.7 (5.0)	27.5 (5.0)	31.0 (5.4)	28.3 (5.2)	31.4 (5.1)	28.7 (5.1)	32.4 (5.9)	28.5 (5.9)
History of type 2 diabetes (%)	17.0	10.7	19.8	8.6	19.4	9.9	20.1	6.5
History of hypertension (%)	46.2	35.7	34.6	25.0	42.0	28.3	40.0	24.8
Median (interquartile range) aspartate transaminase (IU/L)	24 (19-33)	20.7 (17-25)	29 (22-40)	23 (20-28)	29 (22-40)	21 (18-27)	32 (24-47)	22 (19-27)
Median (interquartile range) alanine transaminase (IU/L)	30 (20-49)	21 (16-30)	37 (25-56)	25 (18-33)	35 (23-54)	20 (15-28)	46 (29-69)	23 (17-31)
Mean (SD) total cholesterol (mmol/L)	5.41 (1.06)	5.43 (1.03)	5.31 (1.16)	5.35 (1.10)	5.40 (1.01)	5.37 (0.97)	5.23 (1.24)	5.16 (1.16)
Mean (SD) HDL cholesterol (mmol/L)	1.31 (0.34)	1.43 (0.38)	1.21 (0.31)	1.36 (0.36)	1.27 (0.32)	1.42 (0.37)	1.25 (0.36)	1.43 (0.77)
Mean (SD) systolic blood pressure (mm Hg)	132.8 (15.2)	131.7 (15.7	138.2 (17.5)	136.7 (17.7)	131.7 (13.6)	129.2 (14.2)	134.3 (14.8)	131.9 (15.8)

HDL=high density lipoprotein.
*After imputation of missing as non-smokers. For laboratory values, outlier values greater than mean+3×standard deviation were excluded (mean and standard deviation computed separately in participants with and without NAFLD separately).

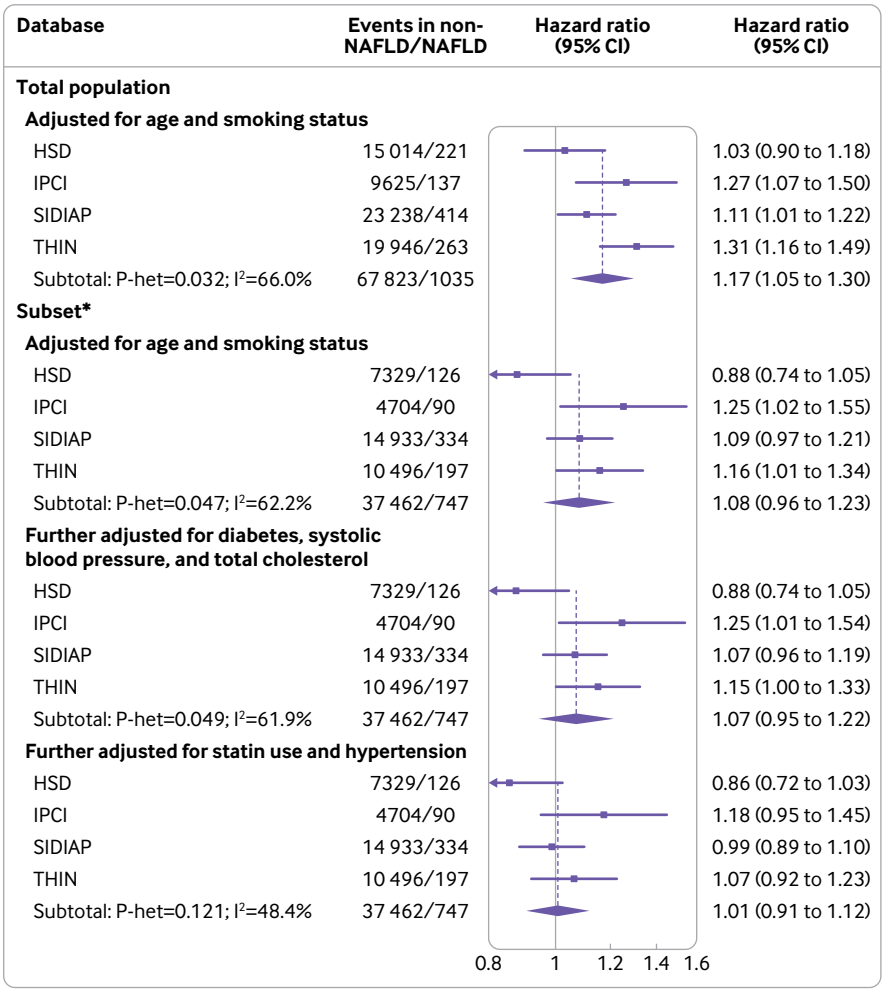

Fig 1 | Hazard ratios (95% confidence intervals) for acute myocardial infarction in participants with non-alcoholic fatty liver disease (NAFLD). Data for age, sex, and smoking status were available for 120 795 participants with NAFLD and 9 647 644 matched participants without NAFLD. *Subset analyses were restricted to participants with data for age, smoking status, type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension (86 098 participants with NAFLD and 4 664 988 matched controls, respectively). Analyses were progressively adjusted for age, smoking status, type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension. Weights are from random effect meta-analysis and are inversely proportional to the variance of the estimated hazard ratios (therefore proportional to the number of events contributing the hazard ratios). Statin use in The Health Improvement Network (THIN, United Kingdom) was missing and therefore imputed. HSD=Health Search Database (Italy); IPCI=Integrated Primary Care Information (Netherlands); SIDIAP=Information System for Research in Primary Care (Spain); P-het=P value for heterogeneity

matched controls we found that a recorded diagnosis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) is more weakly associated with any excess risk of acute myocardial infarction (AMI) and stroke beyond known associated risk factors. In the current study, the age and sex adjusted hazard ratio was around 1.2 rather than 1.6 to 2.0-fold reported in recent meta-analyses of previous cohorts.[9 10] When we adjusted for other covariates in the subset of participants with more complete data on risk factors, the hazard ratio moved towards the null for both AMI and stroke with sequential adjustment for these risk factors. These data suggest that a diagnosis of NAFLD in routine clinical practice across Europe does not necessarily indicate the need for AMI or stroke preventive treatments. Rather, our results suggest that the risk of cardiovascular disease should be assessed in these people in the standard way using risk scores, with no strong case yet to consider NAFLD as a risk enhancer. This means that for people with NAFLD to be identified at high risk, the coexistence of other well known risk factors (eg, diabetes or hypertension, dyslipidaemia) is required, which a reasonable proportion will have, and such risk factors should be dealt with as for usual guideline recommendations. This is analogous to the situation for prediabetes where the risk of cardiovascular disease should be based on usual risk scores without a risk multiplier.[22]

Strengths of this study

Owing to the large scale of the databases used in our study, we were able to match each participant with

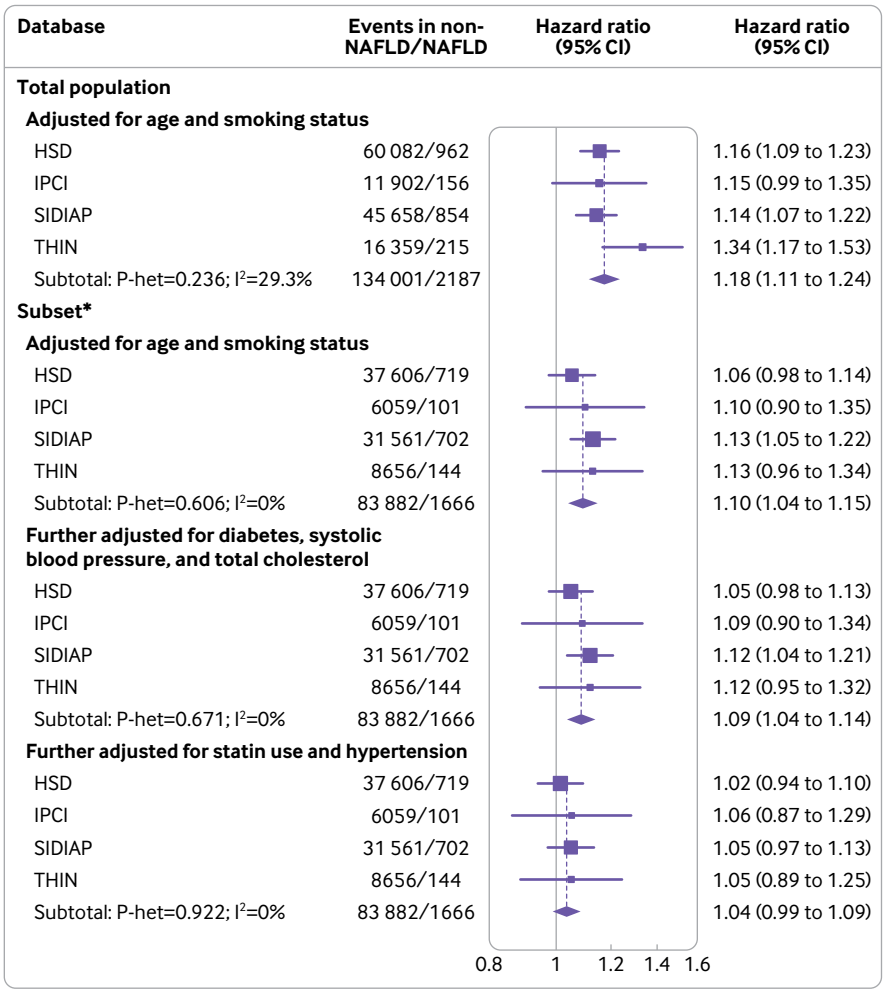

Fig 2 | Hazard ratios (95% confidence intervals) for stroke in participants with non-alcoholic fatty liver disease (NAFLD). Data for age, sex, and smoking status were available for 120 795 participants with NAFLD and 9 647 644 matched participants without NAFLD. *Subset analyses were restricted to participants with data for age, smoking status, type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension (86 098 NAFLD and 4 664 988 matched controls, respectively). Analyses were progressively adjusted for age, smoking status, type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension. Weights are from random effect meta-analysis and are inversely proportional to the variance of the estimated hazard ratios (therefore proportional to the number of events contributing the hazard ratios). Statin use in The Health Improvement Network (THIN, United Kingdom) was missing and therefore imputed. HSD=Health Search Database (Italy); IPCI=Integrated Primary Care Information (Netherlands); SIDIAP=Information System for Research in Primary Care (Spain); P-het=P value for heterogeneity

a recorded diagnosis of NAFLD with several people without such a diagnosis, from the same general practice, sex, and age within five years either way as the participants with NAFLD. We conducted our study concurrently in four European databases holding primary care data that have been extensively used for research, each one with multiple publications, and all part of the EU-Adverse Drug Reactions (ADR) Alliance, which conducts voluntary or mandated European Union-wide post-authorisation safety studies.[13-16 18] Furthermore, other important diagnoses have been validated in these databases, for example AMI,[23] strengthening our hypothesis that these electronic health records capture recording of clinical diagnoses in primary care.

Comparison with previous studies

Our routine care data showed differential, weaker, associations of NAFLD with an excess of incident AMI or stroke outcomes over and above associated risk factors compared with meta-analyses of AMI or stroke event data in previous observation cohorts.[9 10] One potential is that, unlike previous observation cohorts, we comprehensively adjusted for known risk factors for cardiovascular disease when available. We also adjusted using continuous rather than categorical measures, and we considered current lipid lowering treatments. Participants without NAFLD were matched according to the general practice, which limited confounding by social class, something cohort studies have also rarely considered. Social class is an often

overlooked but increasingly important confounder as there are clear gradients in obesity and diabetes risks by social class,[24] factors that predict differences in NAFLD occurrence, suggesting NAFLD is also strongly socially patterned. Social class is also a strong predictor of AMI or stroke events and is now included in several validated risk scores.[25 26] Cardiovascular and NAFLD risk vary by ethnicity, but we were unable to assess this in the current study because these data are not held in the Health Search Database (HSD), Information System for Research in Primary Care (SIDIAP), and Integrated Primary Care Information (IPCI).[27] Although multivariable adjustment took into account confounding for several potential factors (smoking, medical history, obesity), and despite our extensive matching, residual confounding could still be present owing to other factors (such as body mass index (BMI) and high density lipoprotein cholesterol level), which we have not included here, but these omissions would increase rather than nullify hazards. We do, however, recognise that the need to have more complete risk factor data in some of our analyses could have marginally attenuated risk differences between those with and without NAFLD.

Alcohol as confounder

To eliminate confounding from liver disease potentially driven by alcohol, we excluded adults with other chronic liver conditions such as alcoholic liver disease and those with a coded diagnosis of alcohol misuse. Alcohol consumption is difficult to determine accurately in clinical practice and is therefore unreliably recorded in routine care records. A recent major alcohol study combining 83 prospective cohorts in which alcohol consumption was carefully evaluated and recorded, did not show an overall lower risk for total cardiovascular disease with alcohol.[28] Non-fatal AMI risk was slightly lower (hazard ratio 0.94 for 100 g higher alcohol intake weekly), and the risk of all other adverse vascular outcomes including stroke (1.14 for 100 g higher alcohol intake weekly) was higher. Hence, if the participants with NAFLD or NASH in the current study consumed moderate amounts of alcohol more often than their matched counterparts, our results for AMI might have been biased towards the null, but stroke risk should have been biased the other way. That the hazard ratios associated with alcohol are modest and that results for our two main outcomes of AMI and stroke show broadly consistent results, however, suggest any confounding is likely to be minimal.

We recently used these databases to show that the recorded age and sex specific point prevalence of NAFLD between 2007 and 2014 is much lower than expected, with less than 2% of the total number of patients registered in the databases having a recorded diagnosis of NAFLD.[17] It is therefore possible that we did not identify a representative sample of adults with NAFLD. Even if cohort studies have overestimated the prevalence of NAFLD in the general population, many participants might have NAFLD but without a diagnosis made or recorded, and they were included in our population of matched participants. The characteristics of the participants with NAFLD identified in our study are, however, consistent with published cohort studies. In a recent meta-analysis of 86 cohort studies in 22 countries, metabolic comorbidities associated with NAFLD included obesity (51.3%, 95% confidence interval 41.4% to 61.2%), type 2 diabetes (22.5%, 17.9% to 27.9%), and hypertension (39.3%, 33.2% to 45.9%).[29] In our summary data (table 1), average BMI was greater than 30 in three of the electronic health records for NAFLD, average diabetes percentages were around 19%, and the average proportion with hypertension was around 40%, results near identical to the meta-analysis,[29] lending strong external validity to our cohort make-up. We therefore believe that those with coded NAFLD or NASH have been correctly identified as they have all the associated clinical characteristics of the condition and at levels near identical to those proved to have NAFLD using imaging techniques. We accept a proportion in the matched population will have undiagnosed NAFLD but these will be diluted out by others without NAFLD: evidenced by the average characteristics of the matched controls. We also could not determine how doctors diagnosed NAFLD in each case, but these data suggest that those identified did have NAFLD.[17] From a practical point of view, it is not possible to apply a cardiovascular risk multiplier (if appropriate) to a particular condition in people without a diagnosis of that condition. Therefore, despite the low point prevalence, our data represent the pattern of AMI and stroke risk in people with a recorded diagnosis of NAFLD or NASH.

Additional strengths and limitations of this study

To limit heterogeneity across studies, we harmonised code lists for clinical events and ensured that codes in multiple terminologies all mapped to the same unified medical language system concepts. After local data extraction, one analyst formatted and analysed data in the same way for the four databases[13-16] on the European Medical Information Framework remote server. However, we still observed statistically significant heterogeneity across studies, which was only partially accounted for by progressive adjustment. This is probably due to major differences in healthcare systems between the four countries (eg, NAFLD is diagnosed at a more advanced stage in The Health Improvement Network (THIN)) as well as terminology used to record NAFLD and outcomes. Variation in the methods used to diagnose NAFLD and NASH[30 31] and the extent to which coding was completed also contributes to heterogeneity. We recognise that the difference between HSD and the other cohorts was a main contributor to the observed heterogeneity." The HSD findings seemed to be robust on a recheck. Sensitivity analyses on incident AMI including only the other three more congruent cohorts, however, showed similarly low hazards for AMI in participants with NAFLD. Hence conclusions remain the same whether or not data were included from HSD.

Conclusion

Associations of an existing and recorded diagnosis of NAFLD in routine electronic health records with both incident AMI and stroke were modest (hazard ratios around 1.2) in age, sex, and smoking adjusted models. Moreover, in the cohort where we had more complete data on cardiovascular risk factors, hazard ratios for AMI and stroke were attenuated with adjustment for known cardiovascular risk factors and were null in adjusted models. Thus, NAFLD was not meaningfully associated with the outcomes investigated in our study. A diagnosis of NAFLD does warrant risk assessment for the stage of liver disease, and behaviour and lifestyle advice not only for reduction of liver fat but also for benefits of weight loss on AMI and stroke risk factors, including lipids, systolic blood pressure, and the development of diabetes. Among the large numbers of patients with NAFLD, some, if not many, could be at increased risk of AMI and stroke outcomes. Further study is, however, needed to identify such people and quantify that risk.

For the time being, it should not be assumed that people with a diagnosis of NAFLD are automatically at increased risk of AMI or stroke. Rather, it is important to do a cardiovascular risk assessment in people with a diagnosis of NAFLD, in addition to checking for undiagnosed diabetes. Presently, such cardiovascular risk assessment should be carried out in the same way as for the general population.

AUTHOR AFFILIATIONS

[1]Real World Evidence and Epidemiology, GlaxoSmithKline, Uxbridge, Middlesex, UK

[2]Worldwide Research and Development, Pfizer, Target Sciences, Groton, CT, USA

[3]Department of Medical Informatics, Erasmus University Medical Centre Rotterdam, Rotterdam, Netherlands

[4]Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain

[5]Pharmaco- and Device Epidemiology, Centre for Statistics in Medicine, NDORMS, University of Oxford, Oxford, UK

[6]IQVIA, Kings Cross, London, UK

[7]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[8]Health Search, Italian College of General Practitioners and Primary Care, Firenze, Italy

[9]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA

[10]Diabetes Research Centre, University of Leicester, Leicester, UK

[11]GlaxoSmithKline, Medicines Research Centre, Stevenage, Hertfordshire, UK

[12]Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, UK

[13]Human Genetics, GlaxoSmithKline, Collegeville, PA, USA

[14]Barts Liver Centre, Blizard Institute, Queen Mary, University of London, London, UK

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Contributors: MA, AKL, JvdL, PA, PE, SK, DW, WA, and NS designed the study. TDS, DP-A, DA, AP, FL, MM, and PR extracted data and PR also transformed data and performed some of the data analysis. MA, ND, and CC-M analysed data. All authors interpreted the results. NS, MA, and WA wrote manuscript. All authors edited the manuscript and approved the final version for submission. WA and NS contributed equally to the study and are the guarantors. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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www.icmje.org/coi_disclosure.pdf and declare: MA reports being contracted by SRG to work for GlaxoSmithKline and received a salary from GSK, including bonus. JF-B and DW are paid employees at GlaxoSmithKline and receive salaries, including bonuses. AKL is a paid employee at Pfizer and receives a salary, including bonus. DP-A reports unrestricted research grants from UCB, Amgen, and Servier, and consultancy fees from UCB Pharma paid to his department. DA reports as a paid employee of IQVIA has provided consultancy and advice to many pharmaceutical companies on undertaking outcomes studies using real world evidence. PE and SK report they are paid employees and stock holders of GlaxoSmithKline. NS reports personal fees from AstraZeneca, Amgen, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Janssen, and Sanofi and a grant from Boehringer Ingelheim. WA reports consultancy and sponsored lectures from Gilead, GlaxoSmithKline, Intercept IQVIA, and UCB Pharma.

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Data sharing: No additional data available.

The lead authors (WA and NS) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Supplementary information: additional tables and figures