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Original Article

Investigating the Effect of Metabolic Phenotypes on Health Events in Alcoholic and Nonalcoholic Fatty Liver Disease

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Abstract

Background and Aims: Metabolic dysfunction and obesity commonly coexist with both alcoholic and nonalcoholic fatty liver disease (AFLD and NAFLD). The association of AFLD and NAFLD with incident diseases in individuals with different metabolic phenotypes are unclear. ***Methods:*** UK Biobank study participants were screened for the presence of fatty liver at baseline. Body mass index and metabolic dysfunction were used to define metabolic phenotypes. Cox regression model was performed to examine the associations of AFLD and NAFLD with incident significant liver diseases (SLDs), cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and cancers, respectively. ***Results:*** A total of 43,974 AFLD and 103,248 NAFLD cases were identified. Both AFLD and NAFLD were associated with an increased risk of diseases of interest. The effects were amplified by obesity and metabolic abnormalities and modified by metabolic phenotypes. Compared to individuals free of fatty liver and with phenotype of metabolically healthy-normal weight, AFLD [hazard ratio (HR) 3.27; 95% CI: 1.95–5.47)] and NAFLD (HR 2.25; 95% CI: 1.28–3.94) cases with phenotype of metabolically obese-normal weight had the greatest risk of SLDs. For CVDs, CKDs, and cancer, the greatest risks were detected in AFLD and NAFLD cases with phenotype of metabolically obese-overweight/obesity. In this subpopulation, AFLD and NAFLD conferred a 2.75-fold (95% CI: 2.32–3.25) and 4.02-fold 95% CI: (3.64–4.43) increased risk of CVDs, 4.37-fold 95% CI: (3.38–5.64) and 6.55-fold 95% CI: (5.73–7.48) increased risk of CKDs, and 1.19-fold 95% CI: (1.08–1.27) and 1.21-fold 95% CI: (1.14–1.28) increased risk of cancers, respectively. ***Conclusions:*** Metabolic phenotypes modified the association of AFLD and NAFLD with intrahepatic and extrahepatic diseases.

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Introduction

Fatty liver disease (FLD) includes two distinct histological phenotypes [alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD)]. While AFLD and NAFLD differ in the prevalence and risk factors, they share many aspects in common including histological features and activation of pathways linked to disease development.[1,2] AFLD and NAFLD are becoming the most common chronic liver diseases worldwide,[3,4] and are not as benign as previously thought.[5] They can progress from simple steatosis to steatohepatitis with or without fibrosis, and eventually cirrhosis, liver failure, and hepatocellular carcinoma.[6,7]

NAFLD is closely associated with obesity and metabolic syndrome and was deemed to be a multisystem disease given its association with an increased risk of developing extrahepatic chronic diseases.[8–11] The health effect of NAFLD on intrahepatic outcomes can be modified by metabolic traits,[12] but the modifying effect on extrahepatic outcomes remains unknown. Obesity and metabolic disturbance are also commonly observed in AFLD,[13,14] suggesting that excessive alcohol use and metabolic phenotypes may interact in AFLD progression.[15] In this context, assessing the health effect of AFLD without consideration of metabolic phenotypes and designating excess alcohol intake as the major culprit of the consequences of AFLD might be inappropriate. In this study, which leveraged the data of UK Biobank study, we aimed to assess the impacts of AFLD and NAFLD accompanying with different metabolic phenotypes on new-onset significant liver

Keywords: AFLD; NAFLD; Obesity; Metabolic dysfunction; Metabolic phenotype.
Abbreviations: AFLD, alcoholic fatty liver disease; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; FLD, fatty liver disease; FLI, fatty liver index; MetS, metabolic dysfunction score; MHC, metabolic healthy control; MHNW, metabolically healthy-normal-weight; MHO, metabolically healthy-overweight; MONW, metabolically obese-normal-weight; MOO, metabolically obese-overweight; NAFLD, nonalcoholic fatty liver disease; SLD, significant liver disease; T2D, type 2 diabetes.

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diseases (SLDs), cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and cancers.

Methods

Study participants

The study was conducted using the UK Biobank Resource and had the application number 58,484. The UK Biobank study design and population have been detailed previously.[16] As there were no imaging or histological data on the liver, we calculated the fatty liver index (FLI) for each participant.[17] The FLI, which incorporates body mass index (BMI), waist circumference, and serum triglyceride and γ-glutamyl transferase levels, is a simple and accurate marker of human fatty liver. It has been externally validated for sensitivity and specificity.[18–20] Individuals with FLIs ≥60 were defined as fatty liver cases; those with FLIs <30 were deemed to be free of fatty liver.[21] Participants who were missing data on alcohol consumption and FLI-related variates were excluded (Supplementary Fig. 1).

Definitions of alcoholic and nonalcoholic fatty liver

Total pure alcohol intake in grams was calculated by multiplying the average number of alcoholic drinks consumed each week by the average grams of alcohol contained in each type of drink (Supplementary Table 1), determined using the UK Food Standard Agency's guidelines[22] and the total was divided by 7 days to provide mean daily alcohol intake. We defined ≥30 g/day for men and ≥20 g/day for women as excess alcohol intake. Individuals who both had excessive drinking and fatty liver were defined as AFLD. In contrast, individuals who with fatty liver but without excess alcohol intake were defined as NAFLD (Supplementary Fig. 1).

Definitions of overweight/obese and metabolic dysfunction score

Participants who had BMIs of 18.5–24.9, 25–29.9, or ≥30 kg/m^2 were defined as normal weight, overweight, and obesity, respectively. The metabolic dysfunction score (MetS) ranged from 0 to 3, and indicated the number of conditions presenting at baseline, which included type 2 diabetes (T2D), hypertension, and dyslipidemia.[23] The diagnostic criteria for T2D, hypertension, and dyslipidemia are shown in Supplementary Table 2. Individuals with a MetS = 0 and >0 were defined as metabolically healthy and metabolically obese, respectively.

Outcome data

We used the International Classification of Disease version 10 (ICD-10) codes to identify incident diseases (Supplementary Table 3). As SLD is a broad term involving a set of liver-related outcomes, in this study, we considered compensated and decompensated cirrhosis, liver transplantation, hepatocellular carcinoma (HCC), and unspecific liver cancer as the SLDs, according to the latest expert consensus.[24] We excluded SLD cases with extrahepatic etiologies. For example, ascites may be caused by cirrhosis, but there are other causes of nonhepatic ascites such as heart failure or malignancy. We identified the prevalent diseases using both ICD-10 and ICD-9 codes, as well as self-reported disease history, and excluded those participants with a history of any of the interested diseases at baseline (e.g., cirrhosis, viral hepatitis, and stroke, Supplementary Table 3). The category of cancer includes all cancer sites except for HCC and unspecific liver cancer.

Statistical analysis

Continuous variables were reported as means with standard deviations and categorical variables were reported as frequencies (percentages). We used Student's *t*-tests, Mann-Whitney U tests, χ^2 tests, and Fisher's exact tests, where appropriate, to compare the differences between people with and without fatty liver. We conducted Cox regression analyses to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of AFLD and NAFLD with incident health events. When we analyzed the associations of AFLD and NAFLD with cancer, HCC was excluded. Age at enrollment, sex, education, assessment center, household income, smoking status, and physical activity were adjusted in the Cox models.

First, we separately assessed the effect of AFLD and NAFLD on incident health events of SLDs, CVDs, CKDs, and cancer. Second, we assessed the health effect of AFLD and NAFLD among those with different BMI. In this analysis, individuals were assigned to four groups. Participants free of fatty liver and with BMI of 18.5–24.9 kg/m^2 were the reference group. The other three groups included participants of normal weight who had fatty livers, were overweight, or were obese. Third, we assessed the health effects of AFLD and NAFLD among those with various levels of MetS. Individuals were divided into five groups. The reference group was free of both fatty liver and metabolic dysfunction. The other four groups had fatty liver with MetS ranging from 0 to 3. Finally, we categorized the participants to investigate the interaction between BMI and metabolic dysfunction. Due to the small sample size, we combined overweight and obese individuals and to form five distinct metabolic phenotypes, which were metabolically healthy controls (MHC, no fatty liver, a MetS score of 0 and normal weight), metabolically healthy-normal weight (MHNW, fatty liver with a MetS score of 0 and normal weight), metabolically healthy-overweight (MHO, fatty liver with a MetS score of 0 and overweight/obese), metabolically obese-normal weight (MONW, fatty liver with a MetS score >0 and normal weight), and metabolically obese-overweight (MOO, fatty liver with an MetS score >0 and overweight/obese).[25] The MHC phenotype was the reference group. As the fatty liver was defined as an FLI ≥60, the fatty liver cases with normal weight may have higher serum triglyceride and γ-glutamyl transferase (GGT) levels than overweight/obese individuals. That may introduce biases into effect estimates in the analyses of BMI and metabolic phenotypes. We thus also adjusted the FLI-related variables, triglyceride and GGT, in the Cox models. Waist circumference was not included due to the high correlation with BMI (p=0.814, p<2E−16).

Sensitivity analysis

First, we excluded the participants who had a follow-up of <6 months. Second, we integrated the AFLD and NAFLD cases as a whole and then re-analyzed the associations of FLD with the incidence of health events. Third, to avoid biases of misclassification in SLDs, we analyzed the associations of AFLD and NAFLD with HCC, which has an ICD-10 code of C22.0. In this analysis, we integrated AFLD and NAFLD as a whole owing to the individually small case number of HCC. The statistical analysis was conducted with R (v3.6.3; R core team, Vienna, Austria).

Results

Baseline characteristics of study participants

Of 283,823 eligible individuals, 73,677 had excess alcohol intake and 210,146 did not (Supplementary Fig. 1). A total of 43,974 AFLD and 103,248 NAFLD cases were identified (Table 1). The baseline characteristics were significantly dif-

Table 1. Baseline characteristics of the study participants

Characteristics	Participants with excess alcohol intake			Participants without excess alcohol intake		
	Non-AFLD	AFLD	*p* values	Non-NAFLD	NAFLD	*p* values
Sample size, *n*	29,703	43,974		106,898	103,248	
Female	22,414 (75.5)	9,870 (22.4)	<0.001	81,165 (75.9)	37,451 (36.3)	<0.001
Age in years, mean (SD)	55.4 (8.0)	57.5 (7.7)	<0.001	55.8 (8.3)	58.0 (7.8)	<0.001
Education score, median (IQR)	6.1 (1.9, 14.7)	9.0 (2.9, 21.2)	<0.001	6.7 (2.2, 15.8)	10.8 (3.7, 23.3)	<0.001
Average total household income before tax (£)			<0.001			<0.001
Less than 18,000	3,691 (14.0)	7,729 (19.6)		16,433 (18.0)	22,846 (26.0)	
18,000 to 30,999	5,744 (21.7)	9,533 (24.1)		22,087 (24.2)	22,977 (26.2)	
31,000 to 51,999	7,327 (27.7	10,824 (27.4)		24,813 (27.2)	22,167 (25.2)	
52,000 to 100,000	7,079 (26.8)	8,923 (22.6)		21,645 (23.7)	16,218 (18.5)	
Greater than 100,000	2,589 (9.8)	2,515 (6.4)		6,359 (7.0)	3,620 (4.1)	
Smoking status			<0.001			<0.001
Never	12,801 (43.2)	15,060 (34.4)		69,268 (65.0)	53,829 (52.4)	
Former	12,314 (41.5)	21,836 (49.8)		29,678 (27.8)	39,191 (38.1)	
Current	4,508 (15.2)	6,924 (15.8)		7,651 (7.2)	9,744 (9.5)	
Physical activity			<0.001			<0.001
0–1 day/week	4,739 (16.4)	10,248 (24.3)		17,219 (16.7)	24,018 (24.9)	<0.001
2–4 days/week	11,614 (40.2)	16,215 (38.4)		42,309 (41.2)	38,123 (39.5)	<0.001
5–7 days/week	12,505 (43.3)	15,737 (37.3)		43,277 (42.1)	34,317 (35.6)	<0.001
BMI categories			<0.001			<0.001
18.5–24.9	22,252 (74.9)	1,505 (3.4)		79,346 (74.2)	2,185 (2.1)	
≥25.0	7,451 (25.1)	42,469 (96.6)		27,552 (25.8)	101,063 (97.9)	
Metabolic dysfunction score			<0.001			<0.001
0	25,482 (85.8)	25,412 (57.8)		90,423 (84.6)	57,923 (56.1)	
1	3,657 (12.3)	13,397 (30.5)		13,766 (12.9)	29,757 (28.8)	
2	526 (1.8)	4,388 (10.0)		2,458 (2.3)	12,436 (12.0)	
3	38 (0.1)	777 (1.8)		251 (0.2)	3,123 (3.0)	
Mean ALT in U/L, median (IQR)	16.2 (13.2, 20.1)	28.1 (21.5, 38.0)	<0.001	16.1 (13.1, 20.1)	25.7 (19.7, 34.6)	<0.001
Mean AST in U/L, median (IQR)	23.0 (20.1, 26.7)	27.8 (23.6, 33.8)	<0.001	22.8 (19.9, 26.4)	26.1 (22.3, 31.1)	<0.001
Mean ALP in U/L, median (IQR)	71.3 (59.5, 85.1)	81.6 (69.1, 96.4)	<0.001	75.0 (62.4, 89.6)	85.0 (71.8, 101.0)	<0.001
Mean GGT in U/L, median (IQR)	20.4 (16.2, 26.8)	51.2 (35.2, 80.6)	<0.001	18.1 (14.6, 23.6)	37.5 (27.0, 56.0)	<0.001
Mean TRG in mmol/L (SD)	1.1 (0.4)	2.4 (1.2)	<0.001	1.1 (0.5)	2.4 (1.2)	<0.001

Values are numbers (%) unless indicated otherwise. AFLD, alcoholic fatty liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, λ-glutamyl transferase; IQR, inter-quantile range; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation; TRG, triglyceride.

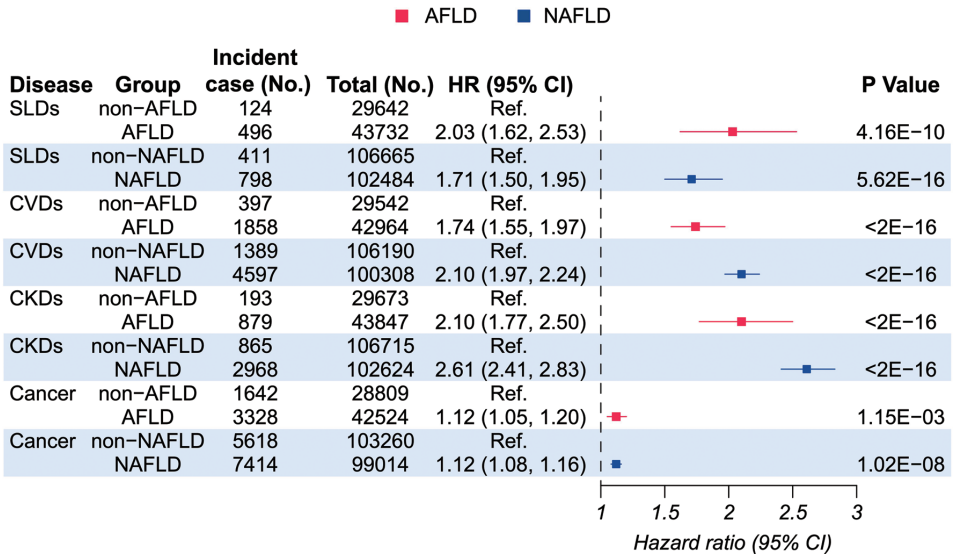

Fig. 1. Association of alcoholic and nonalcoholic fatty liver disease (AFLD and NAFLD) with incidence of significant liver diseases (SLDs), cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and cancer.

ferent between individuals with and without fatty liver, regardless of alcohol intake. People with fatty livers were more likely to be male, older, smokers, physically inactive, socioeconomically deprived, overweight, and have metabolic dysfunction compared with those without fatty livers. Individuals with fatty liver had higher serum liver enzyme, triglyceride, cholesterol, and glucose levels and higher blood pressure than those without fatty livers (Table 1).

Health effects of AFLD and NAFLD

During the follow-up to Mar 31, 2017 (median 8.2 years of age; IQR, 7.5–8.9), 1,829 individuals developed SLDs, 8,241 developed CVDs, 4,905 developed CKDs, and 18,002 developed cancer. Compared with participants without FLD, those with FLD, regardless of alcohol use, had a significantly increased risk of all interested diseases (Fig. 1).

Overweight/obesity and metabolic syndrome exacerbate the health effects of AFLD and NAFLD

The health effects of AFLD and NAFLD were both significantly amplified by overweight/obesity (Fig. 2). For SLDs, CVDs, and CKDs, the greatest risks were detected in obese fatty liver cases, regardless of alcohol use, compared with participants free of fatty liver and of normal weight. The association of BMI with the risk of disease was dose dependent. Compared with the reference group, the multivariable adjusted HR of NAFLD patients for CVDs increased from 1.46 (95% CI: 1.17–1.82) in the normal weight group to 2.24 (95% CI: 2.07–2.43) in the obese group (*p*-value for trend <2E−16). An exception was found in the AFLD group, in which the normal weight participants had the greatest risk of SLDs. For cancer, the effects of AFLD and NAFLD were more significant in normal-weight individuals than in overweight/obese individuals (Fig. 2). However, the effect estimates were either not significant or had high uncertainty. The effect estimates of both AFLD and NAFLD were comparable in overweight and obese cases.

Figure 3 shows the association of AFLD and NAFLD with incident health events in participants who differed in the number of metabolic abnormalities. Compared with individuals who were free of both fatty liver and metabolic dysfunction, the fatty liver patients, regardless of alcoholic or nonalcoholic type, had significantly increased risk of incident events of SLDs, CVDs, CKDs, and cancer. The risks were elevated with the increased number of concomitant metabolic abnormalities. For example, compared with the healthy reference patients, the effect estimates for SLDs increased from 1.86 (95% CI: 1.43–2.41) in the AFLD cases free of metabolic dysfunction to 5.62 (95% CI: 3.61–8.74) in those who had three metabolic abnormalities (*p*-value for trend <2E−16).

Association of AFLD and NAFLD with incident health events were modified by metabolic phenotypes

The effects of AFLD and NAFLD on incident health events varied among individuals with different metabolic phenotypes (Fig. 4). For SLDs, the effect estimates of both AFLD and NAFLD were more significant in individuals with metabolic dysfunction than those without metabolic dysfunction (MONW vs. MHNW and MOO vs. MHO). The synergistic effect of metabolic dysfunction was remarkably amplified in the normal weight individuals. The most pronounced effects of AFLD and NAFLD were both found in individuals had phenotype of MONW.

For CVDs and CKDs, the most pronounced risks were observed in fatty liver cases with the MOO phenotype. The synergistic effect of metabolic dysfunction was more significant than that of overweight. The effect estimates of both AFLD and NAFLD, regardless of BMI, were more remarkable in subpopulations with metabolic dysfunction than those without metabolic dysfunction (MONW vs. MHNW and MOO vs. MHO). In metabolically healthy people, the effect estimates of both AFLD and NAFLD were comparable between overweight and normal-weight individuals (MHO vs. MHNW).

For cancer, the effect estimates were much weaker than those for the other three diseases. Although the most significant risk was found in fatty liver cases with the phenotype of MONW, the effect estimates were either marginally significant or nonsignificant because of the small sample size in this subpopulation. In obese individuals, metabolic dysfunction had a significant synergistic effect (MOO vs. MHO) on cancer risk. A similar phenomenon was observed in individuals

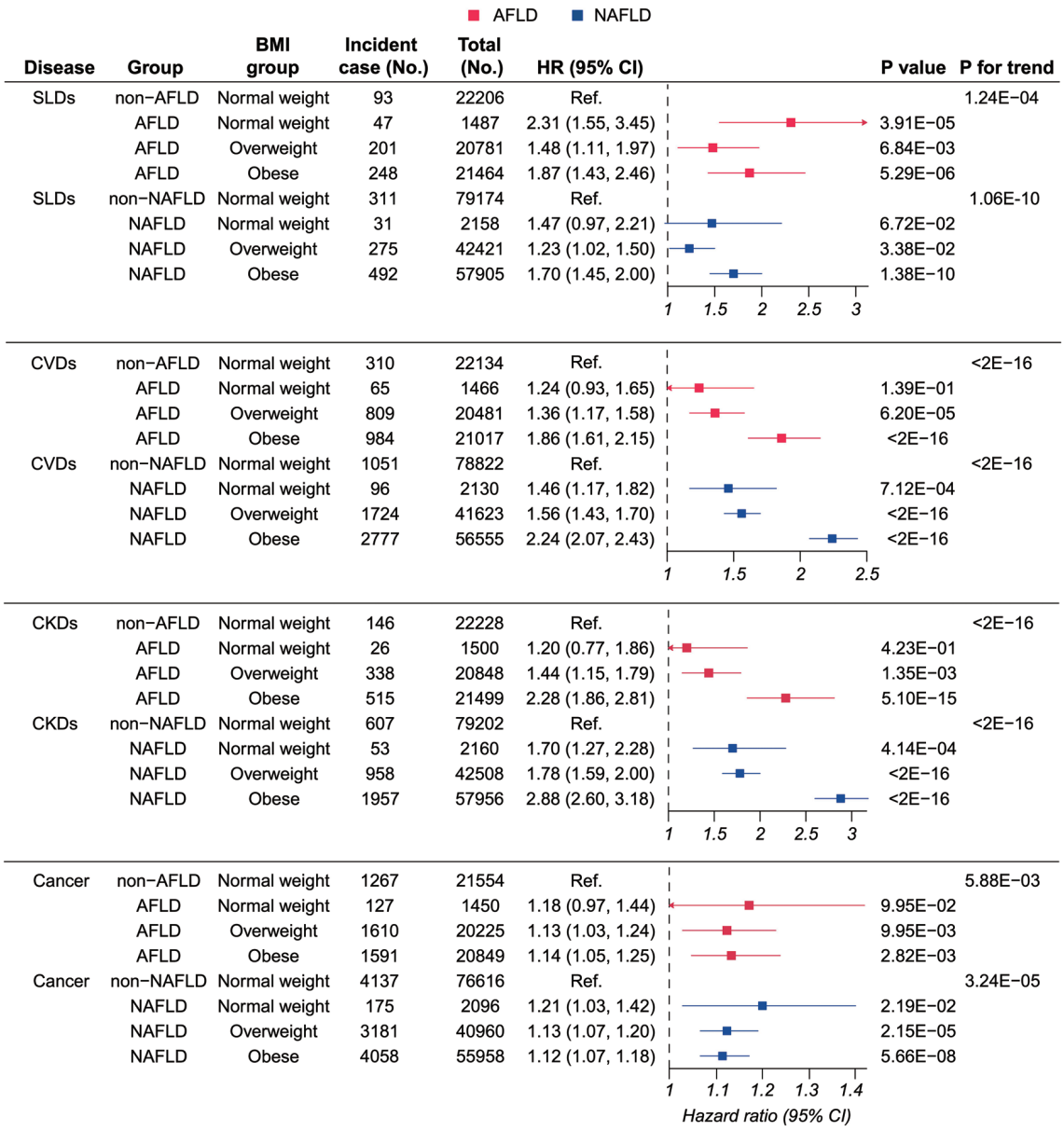

Fig. 2. Association of alcoholic and nonalcoholic fatty liver disease (AFLD and NAFLD) with incidence of significant liver diseases (SLDs), cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and cancer, considering body mass index. Normal weight individuals without fatty liver were the reference group.

with normal weight (MONW vs. MHNW). However, the effect estimates were statistically nonsignificant or had high uncertainty (Fig. 4).

Results of the sensitivity analyses

While nuances of the effect estimates, the results from participants who had a follow-up >6 months and from the FLD cases were consistent with that of our main results (Supplementary Figs. 2–9). We identified 170 HCC cases and observed a more than two-fold increase in the HCC risk among FLD cases (Supplementary Fig. 10). In the subgroup analysis, FLD cases with obesity, had MetS=3, and with metabolic phenotype of MOO had the greatest risk of HCC (Supplementary Figs. 11–13).

Discussion

In this large-scale cohort study, we found that both AFLD and NAFLD were significantly associated with an increased risk of incident health events, including SLD, CVD, CKD, and cancer. The associations were modified differently by metabolic phenotypes and diverse patterns from disease to disease.

Overweight/obesity, metabolic dysfunction, and excess alcohol intake commonly coexisted in fatty liver cases.[13,26] In line with our study, recent evidence suggests harmful synergistic effects of obesity and metabolic dysfunction on the risk of future disease in fatty liver cases.[26,27] Moreover, we found that the patterns of synergistic effect are highly comparable between NAFLD and AFLD cases. The result indicates not only that the two types of fatty liver shared simi-

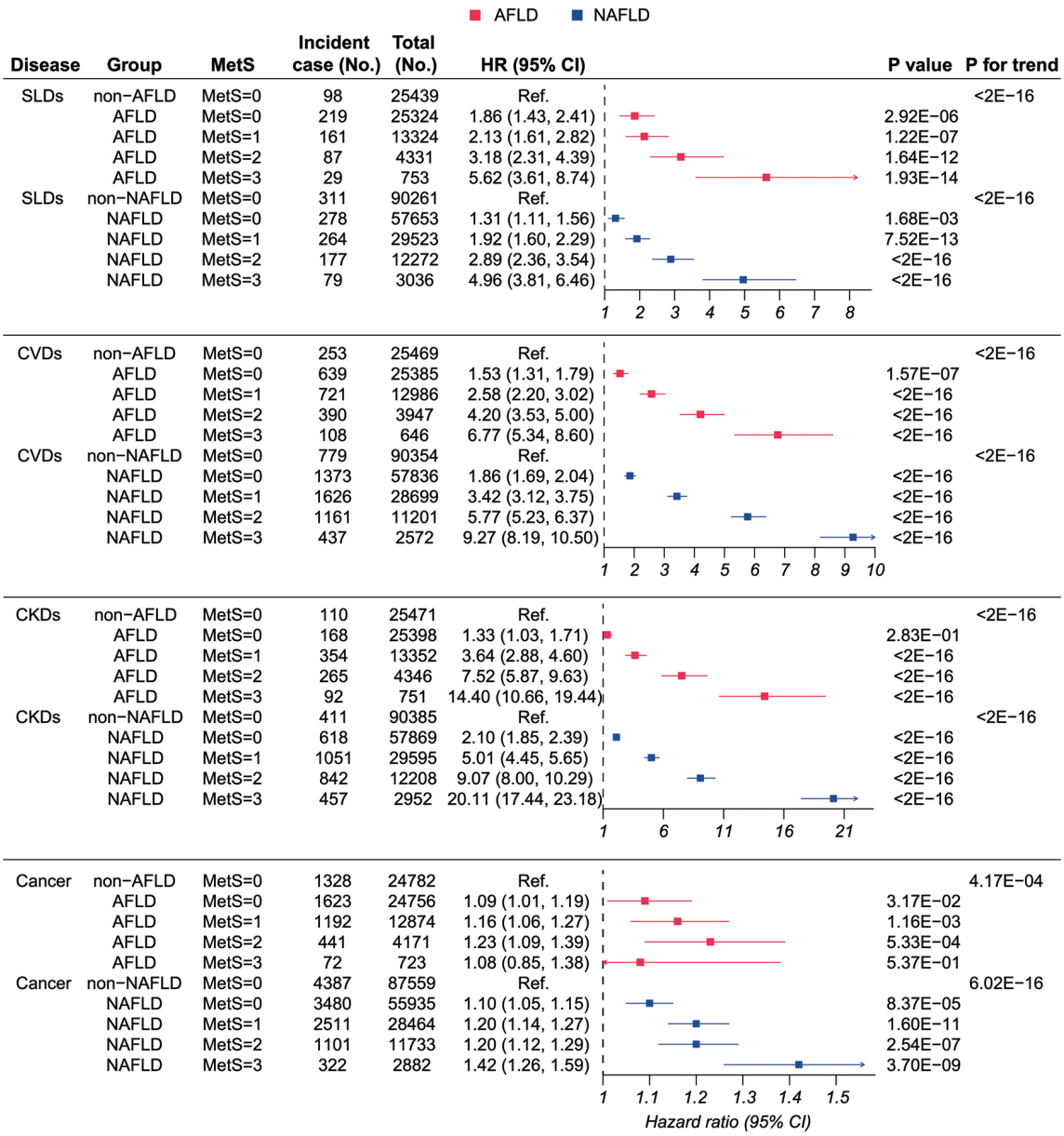

Fig. 3. Associations of alcoholic and nonalcoholic fatty liver disease (AFLD and NAFLD) with incident events of significant liver diseases (SLDs), cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and cancer, considering metabolic dysfunction. Individuals without fatty liver and metabolic dysfunction were the reference. MetS = 0, 1, 2, and 3 indicate the presence of none, one, two, or three types of metabolic abnormalities.

lar health outcomes but also may share common pathogenic mechanisms in the context of obesity and metabolic dysfunction.[28,29] Indeed, given an increasing prevalence of overweight/obese and diabetic alcohol users, it is expected that there will be increasingly more patients who fit neither the typical NAFLD nor the AFLD phenotype, but share features of both disease entities.[26,29] Evidence from genetic association studies also have highlighted that the genetic determinants of the between-individual variability in the predisposition to NAFLD and AFLD are largely shared.[30,31] In conclusion, the overlap in the epidemiologic and genetic architectures suggest that AFLD and NAFLD might be spectra of the same condition, namely, fatty liver disease.[28]

NAFLD patients with normal weight had increased all-cause mortality compared with overweight patients.[32] However, there was less evidence for other liver-related health events. Our findings indicated that the MONW group had higher risks for SLDs than the MOO group in both AFLD and NAFLD patients, which supplements previous studies. One explanation is that lean NAFLD patients are initially more metabolically flexible and have better liver histology. Over time, the metabolic flexibility is lost in patients of normal weight, and the disease progresses to clinical outcomes over a period similar to that of overweight or obese patients.[33] However, the current explanation for the worse outcomes of FLD patients with normal weight is not adequate and needs further study. Interestingly, in our study, we identified a small proportion of fatty liver cases in normal weight patients who

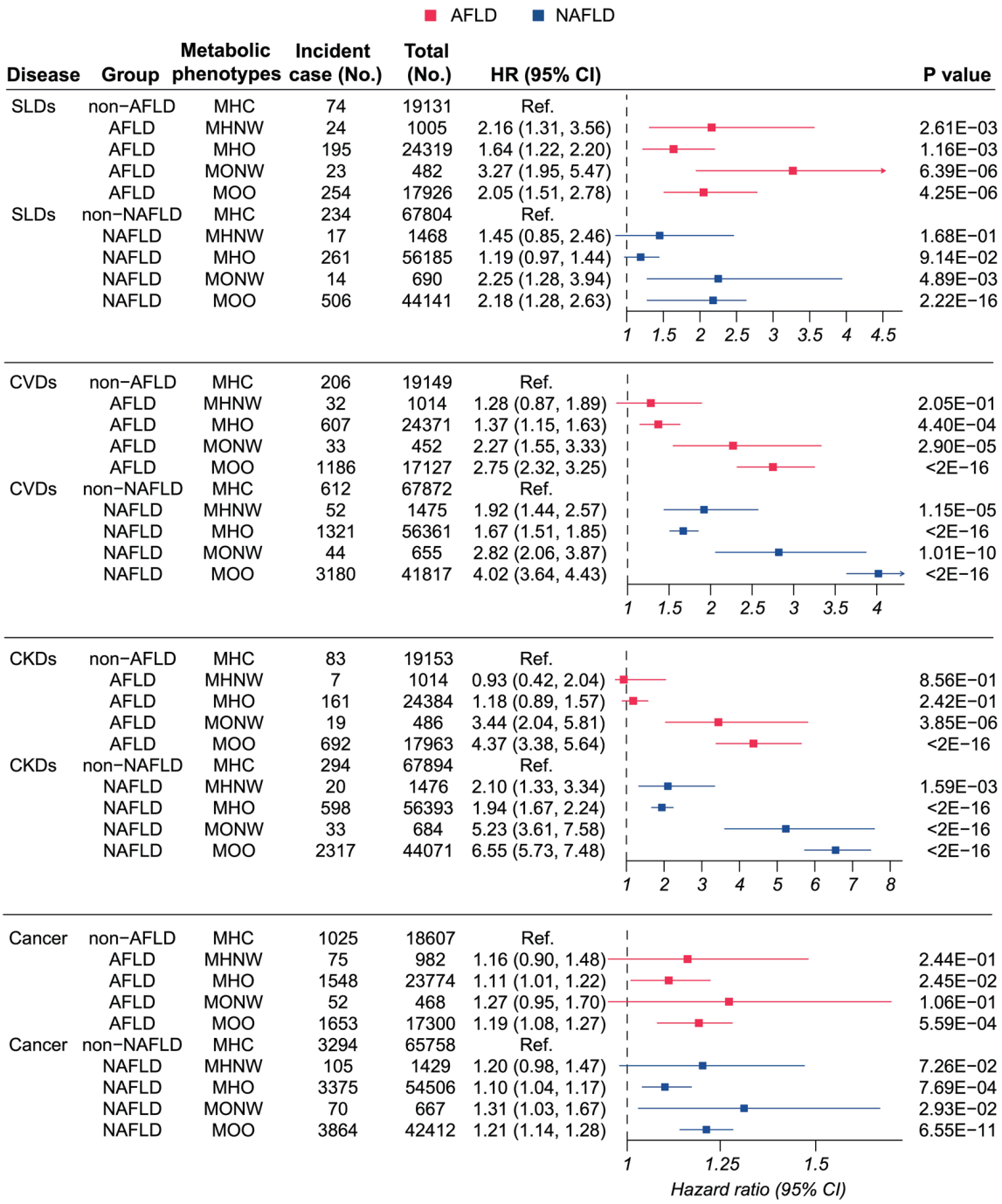

Fig. 4. Associations of alcoholic and nonalcoholic fatty liver disease (AFLD and NAFLD) with incident events of significant liver diseases (SLDs), cardiovascular diseases (CVDs), chronic kidney diseases (CKDs), and cancer, in individuals with different metabolic phenotypes. Normal weight and metabolically healthy individuals were the reference. MHC, metabolically healthy control; MHNW, metabolically healthy-normal weight; MHO, metabolically healthy-overweight; MONW, metabolically obese-normal weight; MOO, metabolically obese-overweight.

were metabolically healthy. Both AFLD and NAFLD had limited effects on incident health events in that subpopulation. The finding suggests that obesity and metabolic dysfunction may be the major culprits of fatty liver progression. However, future studies are warranted to further elucidate the causes, consequences, and pathological features of this phenotype of fatty liver.

Recently, an international panel of hepatologists recommended a change in name for NAFLD to metabolic dysfunction associated fatty liver disease (MAFLD).[34,35] Although controversies remain,[36] the proposal was widely endorsed by hepatologists.[37,38] The most significant alterations for the renaming is that the exclusion of non-excessive alcohol intake is a prerequisite for MAFLD diagnosis, and obesity along with

a set of metabolic dysfunctions are serve as the diagnostic criteria for MAFLD.[39] In our study, we categorized NAFLD and AFLD into four metabolic phenotypes according to BMI and metabolic dysfunction. Our findings highlight the synergistic effect of obesity and metabolic dysfunction on fatty liver progression, regardless of alcohol consumption, and to some extent justify the renaming from NAFLD to MAFLD.

Our findings also provide strong evidence for fatty liver sub-phenotyping and reveal new insights into fatty liver management, given that the health effect of fatty liver varied among populations with different metabolic phenotypes. For example, we found that metabolic dysfunction conferred a more significant synergistic effect on fatty liver for CVDs and CKDs than overweight. The result suggests that the benefits of screening and prevention for common metabolic dysfunctions might include prevention of CVDs and CKDs in fatty liver patients. Of note, the MHNW, MHO, and MONW phenotypes are probably transient conditions of MOO, if no intervention is introduced.[40,41] The MOO phenotype confers the greatest risk of future disease. An exception was observed in SLDs, for which the phenotype of MONW confers the highest risk. The phenomenon was partly consistent with that of a previous cohort study.[2] The underlying reasons for this stronger association are unclear. One of the possible explanations is that BMI might not be an accurate indicator of body fat distribution.[25] Consequently, a person may have a normal BMI but be muscular and physically unfit, or may be obese but have little accumulation of visceral adipose tissue.[25] Future investigations are needed.

Our study has some limitations. First, fatty liver was diagnosed using biomarker-based FLI. Although the sensitivity and specificity of FLI have been externally validated, liver biopsy is regarded as the gold standard. Second, we analyzed the associations of fatty liver with four disease categories, whereas the inner heterogeneities in each disease groups were not taken into account and needs further elaboration in future. Third, the effect estimates from this type of electronic health record-based study might be compromised by misclassification or under-reporting. However, in this study, we used an expert consensus to identify incident health events, and the results from sensitivity analysis confirmed the robustness of our main results.

In summary, our findings reveal that both AFLD and NAFLD affected incident health events differently depending on the metabolic phenotypes. The effect patterns of AFLD and NAFLD were comparable. Stratification of fatty liver cases, irrespective of alcohol intake, based on metabolic phenotypes can help identify individuals at high risk of significant diseases.

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Conflict of interest

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

Author contributions

Conceived of the study design (HF, TZ, XC), performed the statistical analysis (HF, PZ, ZL, RZ), wrote the manuscript (HF, PZ, ZL), provided critical revisions of the draft and approved the submitted draft (all authors), and guarantors (TZ, ZC). The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical statement

This study was performed under generic ethical approval obtained by UK Biobank from the National Health Service National Research Ethics Service (approval letter ref. 11/NW/0382, June 17, 2011). All participants provided written informed consent to participate in the UK Biobank study.

Data sharing statement

The data that support the findings of this study are available from UK Biobank but restrictions apply to their availability.

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