REPORT

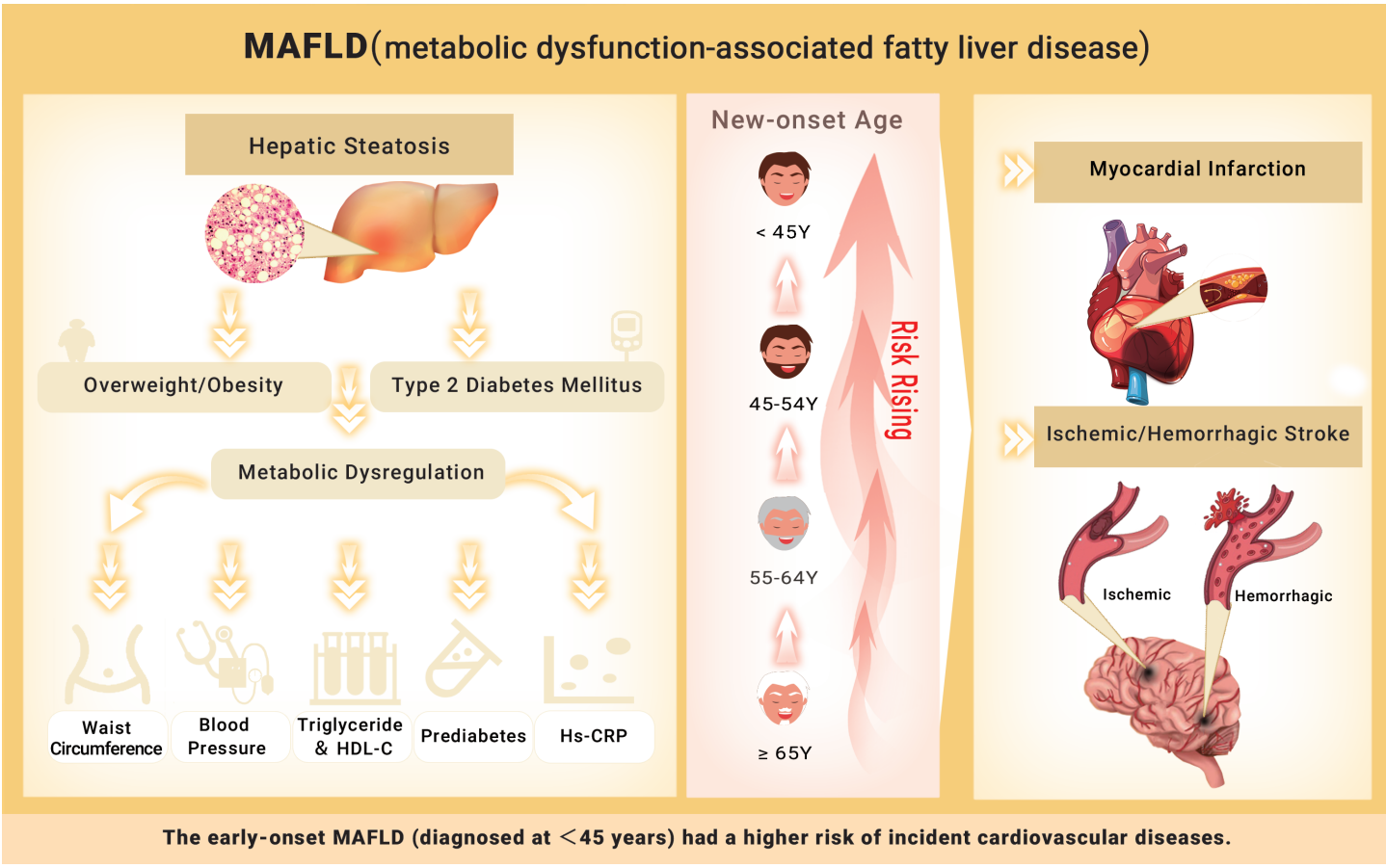
New-onset age of metabolic-associated fatty liver disease and incident cardiovascular diseases: Findings from prospective cohort

Mengyi Zheng,[2,5] Xi Wang,[1,5] Yu Yin,[1] Shuohua Chen,[3] Caixia Guo,[2] Shouling Wu,[4,*] and Yu Yuan[1,*]

*Correspondence: drwusl@163.com (S.W.); yuanyu8@hust.edu.cn (Y.Y.)

Received: August 23, 2023; Accepted: February 6, 2024; Published Online: April 9, 2024; https://doi.org/10.59717/j.xinn-med.2024.100064

GRAPHICAL ABSTRACT



The early-onset MAFLD (diagnosed at ＜45 years) had a higher risk of incident cardiovascular diseases.

PUBLIC SUMMARY

- Onset age of metabolic-associated fatty liver disease (MAFLD) is a key factor of cardiovascular diseases (CVD).
- The incident CVD risks are the highest in the MAFLD patients who were diagnosed at a young age (<45 years).
- The risks gradually declined with each decade increase in MAFLD onset age in Chinese community-based cohort.
- The intensive prevention strategies of CVD and adequate therapy in young MAFLD patients are highlighted.

REPORT

www.the-innovation.org/medicine

New-onset age of metabolic-associated fatty liver disease and incident cardiovascular diseases: Findings from prospective cohort

Mengyi Zheng,[2,5] Xi Wang,[1,5] Yu Yin,[1] Shuohua Chen,[3] Caixia Guo,[2] Shouling Wu,[4,*] and Yu Yuan[1,*]

[1]Department of Occupational and Environmental Health, Key Laboratory of Environment and Health, Ministry of Education and State Key Laboratory of Environmental Health (Incubating), Huazhong University of Science and Technology, Wuhan 430030, China

[2]Cardiovascular Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China

[3]Health Department of Kailuan Group, Tangshan 063000, China

[4]Department of Cardiology, Kailuan General Hospital, Tangshan 063000, China

[5]These authors contributed equally

*Correspondence: drwusl@163.com (S.W.); yuanyu8@hust.edu.cn (Y.Y.)

Received: August 23, 2023; Accepted: February 6, 2024; Published Online: April 9, 2024; https://doi.org/10.59717/j.xinn-med.2024.100064

Citation: Zheng M., Wang X., Yin Y., et al., (2024). New-onset age of metabolic-associated fatty liver disease and incident cardiovascular diseases: Findings from prospective cohort. The Innovation Medicine **2(2)**: 100064.

Whether the early-onset metabolic-associated fatty liver disease (MAFLD) would promote the development of cardiovascular disease (CVD) remains unknown. To investigate the association between MAFLD and the risks of incident CVD across different new-onset age groups, we included 67,160 participants free of MAFLD and CVD at baseline (2006-2007) from the Kailuan study. During the follow-up from baseline to December 31, 2015, 24,772 new-onset MAFLD cases were identified. Each new-onset MAFLD case was matched by one control subject randomly (age ± 1 year, sex-matched). Then 24,772 case-controls were followed up for CVD events. The end of follow-up was the first occurrence of a CVD event, the loss of the follow-up date, or the end of the follow-up (December 31, 2019). Cox proportional hazard regression models with age as the time scale were used to evaluate the hazard ratios (HRs) of incident CVD. During an average follow-up of 8.27 years, 2,881 cases of CVD were identified. After multivariate adjustment, the CVD risk gradually declined with each decade of increase in the MAFLD onset age. MAFLD cases younger than 45 years had the highest CVD risk (hazard ratio, HR, 2.64 [1.87-3.72]), while the CVD risk was attenuated in the 45 to 54 years (HR, 1.41, [1.21-1.65]). However, the HRs in two groups older than 55 years were not statistically significant (HR, 1.10 [0.96-1.25] and 1.05 [0.91-1.22]). Therefore, the onset age of MAFLD is an important predictor of CVD risk. Our finding highlights the importance of intensive prevention, screening, and management of CVD risk among individuals with early-onset MAFLD (diagnosis at <45 years).

INTRODUCTION

To better reflect metabolism-related etiology and disease heterogeneity, a panel of international hepatologists highlighted the need to rename and redefine non-alcoholic fatty liver disease (NAFLD) as metabolic-associated fatty liver disease (MAFLD) in 2020.[1,2] This proposal has been endorsed by many liver associations in Europe,[3] the Asia Pacific,[4] Oceania,[5] Africa,[6] and South America.[7] MAFLD affects approximately a quarter of the global adult population[2] and become the most prevalent chronic liver disease worldwide, causing a substantial burden on public health with global social and economic implications.[8,9] In recent decades, the prevalence of MAFLD in the young population has increased substantially owing to the increasing popularity of unhealthy lifestyles.[2,10] Therefore, MAFLD poses a great threat to public health worldwide, especially in young populations.

Cardiovascular disease (CVD) is the leading cause of disability and mortality in China and worldwide.[11,12] A systematic review[13] revealed that over the past 20 years, the incidence of CVD among young people (18-50 years old) has remained stable or even increased, in contrast to the declining trend among adults over 50 years old. An autopsy study of 2,876 subjects showed that atherosclerosis, the underlying cause of coronary heart disease (CHD), begins and increases rapidly during the 15-34 years.[14] For a long time, traditional prevention efforts of CVD were mainly focused on the middle-aged and elderly population.[15] It is worth noting that future CVD is more likely to occur in young individuals who are always overlooked by the current treatment thresholds.[16,17] Prior studies have demonstrated that early exposure to CVD risk factors (high blood pressure, diabetes, and high lipid levels) would lead to a higher risk of adverse outcomes (e.g., CHD, stroke, and heart failure) compared with exposure later in life.[18] Therefore, early identification and prevention of CVD in the young population is urgently needed.

The early onset age of MAFLD (defined as diagnosis at <45 years) may carry information on both the longer duration of MAFLD and early exposure to CVD risk factors. Recent cohort studies have found that early-onset major metabolic diseases, such as hypertension,[19] diabetes,[20-22] hyperuricemia,[23] and metabolic syndrome,[24] are closely associated with a higher risk of CVD. In addition to systemic metabolic dysfunction, MAFLD represents the hepatic manifestation of a multisystem disorder.[2] A review summarized that the liver injury in NAFLD may lead to an atherogenic profile, the local necro-inflammatory changes of nonalcoholic steatohepatitis may enhance systemic metabolic inflammation, and fibrogenesis may occur concurrently in both the liver and the myocardium.[25] Up to now, there is limited prospective evidence on whether early-onset MAFLD patients have a higher risk of CVD than late-onset MAFLD patients (defined as diagnosis at >55 years), which have important clinical and public health implications. Accordingly, based on a large prospective cohort study, we aimed to examine the association between MAFLD and the risk of incident CVD across different MAFLD onset-age groups.

MATERIALS AND METHODS

Study design and participants

Our study was based on the Kailuan cohort, an ongoing prospective cohort study conducted in Tangshan City, China. The detailed study design and procedures have been described elsewhere.[26] (Supplemental Information: Method and Materials) According to the inclusion and exclusion criteria, a total of 67,160 participants were included at baseline. From baseline to December 31, 2015, 24,772 new-onset MAFLD patients were diagnosed. The date of new-onset MAFLD was defined as the examination date when MAFLD was first determined. Each new-onset MAFLD case was matched by one control subject randomly (age ± 1 year, sex-matched). The follow-up for the incident case started at the time the new-onset MAFLD was identified, while the follow-up of the matched controls started at the same year the incident case was identified. For instance, a new-onset MAFLD case (48 years of age) was identified in 2008. Meanwhile, the matched control was randomly selected from the non-MAFLD participants 47 to 49 years of age when they attended the resurvey in 2008 (both initiated the follow-up in 2008). Ultimately, a total of 24,772 case-control pairs were included in the analyses (Figure S1). The study was conducted with the guidelines of the Declaration of Helsinki and approved by the Kailuan General Hospital Ethics Committee. All participants agreed to participate in the study and provided written informed consent.

Exposure - new-onset MAFLD

New-onset MAFLD was defined according to the recent consensus criteria in 2020 as follows.[1,2] All the participants in the Kailuan cohort undergo screening ultrasonography (PHILIPS HD-15). MAFLD was diagnosed as the presence of hepatic steatosis with one of the following: i) overweight or obese [body mass index (BMI) >23 kg/m^2]; ii) Lean/normal weight (BMI <23 kg/m^2)

with least 2 metabolic risk abnormalities; iii) T2DM. Metabolic risk abnormalities were defined as the presence of at least two metabolic risk abnormalities: (1) waist circumference ≥90/80 cm in Asian men and women; (2) blood pressure ≥130/85 mmHg or specific medications treatment; (3) plasma triglyceride (TG) ≥1.70 mmol/L or specific medications treatment; (4) plasma high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women or specific medications treatment; (5) prediabetes (i.e., fasting glucose levels 5.6 to 6.9 mmol/L); (6) plasma high-sensitivity C-reactive protein (hs-CRP) level >2 mg/L. The homeostasis model assessment of insulin resistance score was unavailable in our study. T2DM was defined as a fasting blood glucose (FBG) level of ≥7.0 mmol/L, the use of an oral hypoglycemic agent or insulin, or a self-reported physician diagnosis (Figure S2). The date of MAFLD onset was defined as the date of examination when MAFLD was first diagnosed. In addition, subjects were classified as early-onset if they were diagnosed at <45 years of age (early-onset MAFLD), and were defined as late-onset if they were diagnosed older than 55 years (late-onset MAFLD).

Outcome - the first occurrence of a CVD event

The primary outcome in our study was the first occurrence of the CVD event during follow-up, and the secondary outcomes were the CVD subtypes including myocardial infarction (MI) and stroke [ischemic stroke (IS) and hemorrhagic stroke (HS)]. Experts determined outcomes according to the International Classification of Diseases, 10th Revision (ICD-10) codes. The specific codes are as follows: MI, I21; IS, I63; HS, I60-I61.[27,28] Information on the major CVD outcomes was retrieved from the Municipal Social Insurance Institution, the Hospital Discharge Register from Kailuan General Hospital, and its 11 affiliated hospitals annually during follow-up. MI was determined based on the patient's typical clinical symptoms, positive electrocardiographic changes, abnormal cardiac biomarkers, and coronary angiography findings according to the World Health Organization's Multinational Monitoring of Trends, Determinants in Cardiovascular Disease criteria[29] and the Fourth Universal Definition of Myocardial Infarction (2018).[30] Stroke was diagnosed according to the World Health Organization criteria based on combined typical neurological signs and neuroimaging imaging examinations, including computed tomographic or magnetic resonance imaging scans.[31] The end of follow-up was the first occurrence of a CVD event, the loss of the follow-up date, or the end of the follow-up (December 31, 2019).

Covariates

Other related variables were collected through self-reported questionnaires, basic anthropometric measurements, and blood tests biennially since 2006. Participants' information on age, sex, educational level, physical activity, smoking status, alcohol intake status, sodium intake, history of diabetes or hypertension, and use of medications (antidiabetic, antihypertensive, or antihyperlipidemic) were collected via face-to-face interviews using a standard questionnaire. The concentrations of FBG, low-density lipoprotein cholesterol (LDL-C), HDL-C, hs-CRP, and alanine aminotransferase (ALT) were measured by a Hitachi 747 auto-analyzer (Hitachi, Tokyo, Japan) on the day of blood collection. Details of data collection and definitions of covariates are shown in the supplemental material (Supplemental Information: Method and Materials).

Statistical analysis

Baseline characteristics were shown as mean standard deviation (SD) for normally distributed continuous variables, median (25th-75th percentiles) for non-normally distributed continuous variables, and percentages N (%) for categorical variables. Continuous variables were compared using analysis of variance, Student's t-tests, or Mann-Whitney U tests, and categorical variables were compared with the chi-squared test.

The new-onset MAFLD participants were divided into four groups based on the age at diagnosis: <45 years, 45-54 years, 55-64 years, and ≥65 years. When the risk of the outcome event does not follow an exponential distribution with increasing age, age is no longer suitable to be included as a covariate in the adjustment model. [32] In this study, the risk of CVD with age was not exponentially distributed. There was a difference in the risk of CVD between a 50-year-old followed for 10 years and a 60-year-old followed for 10 years. Therefore, we used the Cox proportional hazards regression models with age as the underlying time scale[33] to estimate the association of MAFLD with the risk of incident CVD across different MAFLD onset-age groups. This approach takes into account the differences in the effect of follow-up according to age and duration. The multivariable-adjusted model was adjusted for heart rate, uric acid, estimated glomerular filtration rate (eGFR), ALT, smoking status (never, former, or current smoker), alcohol consumption (never, former, light, moderate, or heavy), physical activities (never, occasional, or regular), sodium intake (low, moderate, or high intake), and educational level (high school or beyond, yes/no).

To assess the robustness of our study findings, we further performed several sensitivity analyses: (1) We excluded current drinkers to reduce the influence of alcohol; (2) We excluded participants with hepatitis B, cirrhosis, and cancer to reduce the potential influence; (3) The use of medication (antidiabetic, antihypertensive, or antihyperlipidemic) were adjusted additionally in the Cox proportional hazards regression models; (4) We further conducted similar analyses by excluding participants with the use of medications (antidiabetic, antihypertensive, or antihyperlipidemic) (5) We repeated our analyses of incident CVD using Fine-Gray models instead, which would account for death as a competing risk; (6) As the data did not satisfy the proportional hazards assumption, we further tested the results with the weighted Cox proportional hazards regression models,[34] (7) We excluded the CVD events that occurred within the first year of the follow-up period to minimize potential reverse causation; (8) In addition, we further conducted stratified analyses according to sex; (9) We explored the associations of MAFLD with the risks of fatal or non-fatal CVD events across different new-onset age groups; (10) Given that MAFLD is a new definition updated from NAFLD, we conducted sensitivity analyses among the NAFLD participants; (11) We further conducted the dose-response relations between age at MAFLD diagnosis and the risk of CVD using the %RCS Reg SAS macro program. The reference age was the 10th percentile of each age group, which were 29.1 years, 46.2 years, 55.9 years, and 66.0 years for <45 years, 45-54 years, 55-64 years, and ≥65 years, respectively. The dose-response relations between age at MAFLD diagnosis and the risk of CVD were evaluated by restricted cubic spline, with 4 knots placed at 5th, 35th, 65th, and 95th of the age distribution.

All statistical analyses were conducted using the SAS 9.4 software (SAS Institute, Cary, NC). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 24,772 new-onset MAFLD cases were identified during the average follow-up duration of 6.40 years. The basic characteristics of participants with new-onset MAFLD and their corresponding controls are shown in Table 1. Most variables were significantly different between MAFLD cases and controls (all P values < 0.05), except for physical exercise. Compared with controls, patients with MAFLD had higher levels of heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, BMI, LDL-C, TG, hs-CRP, uric acid, and ALT, a higher prevalence of smoking, alcohol consumption (light, moderate, and heavy), hypertension, diabetes, and use of antihypertensive, antidiabetic, and antihyperlipidemic medications, as well as high sodium intake.

Table 1 also illustrates the basic characteristics of the new-onset MAFLD participants across age groups. There were 5,255 participants at <45 years, 8,027 participants at 45 to 54 years, 7,552 participants at 55 to 64 years, and 3,938 participants at ≥65 years. Specifically, compared with late-onset MAFLD participants, early-onset MAFLD participants had higher ALT levels, with average ALT levels of 22.0 U/L and 17.0 U/L for those under 45 years and over 65 years. Among individuals diagnosed with MAFLD under 45 years, there were higher levels of TG and eGFR, a higher proportion of smoking, alcohol consumption (light and moderate), hepatitis B, high sodium intake, and lack of physical activity. Additionally, the levels of SBP, FBG, LDL-C, hs-CRP, the prevalence of hypertension and diabetes, and the proportion of antihypertensive and antidiabetic medication usage increase with the age group rising.

Table 1. Basic characteristics for the study participants

Variables	Total patients, No. (%) (N = 49,544)			Patients by MAFLD onset age, No. (%)				
	Non-MAFLD (n = 24,772)	New-onset MAFLD (n = 24,772)	*P* Value [a]	<45Y (n = 5,255)	45-54Y (n = 8,027)	55-64Y (n = 7,552)	≥65Y (n = 3,938)	*P* Value [a]
Age, years	53.8 ± 11.7	53.8 ± 11.7	-	37.4 ± 5.6	50.5 ± 2.9	59.4 ± 2.7	71.7 ± 5.2	<0.001
Sex, male	19,466 (78.6)	19,466 (78.6)	-	4,401 (83.7)	5,895 (73.4)	5,798 (76.8)	3,372 (85.6)	<0.001
Heart rate (beats/min)	73.4 ± 10.0	74.1 ± 10.2	<0.001	74.5 ± 9.8	74.2 ± 9.6	73.5 ± 10.4	74.3 ± 11.2	<0.001
SBP (mmHg)	129.1 ± 19.6	134.0 ± 19.4	<0.001	124.5 ± 14.7	131.3 ± 17.6	137.9 ± 19.8	144.9 ± 20.5	<0.001
DBP (mmHg)	82.2 ± 10.7	85.4 ± 10.8	<0.001	83.1 ± 10.0	85.9 ± 10.8	86.6 ± 10.8	84.9 ± 11.1	<0.001
FBG (mmol/L)	5.5 ± 1.4	5.7 ± 1.5	<0.001	5.3 ± 1.0	5.7 ± 1.5	5.8 ± 1.6	5.9 ± 1.7	<0.001
BMI (kg/m^2)	23.3 ± 2.8	25.8 ± 2.7	<0.001	26.2 ± 2.7	25.6 ± 2.6	25.7 ± 2.7	25.6 ± 2.8	<0.001
LDL-C (mmol/L)	2.6 (2.1-3.1)	2.7 (2.2-3.2)	<0.001	2.6 ± 0.8	2.7 ± 0.9	2.8 ± 1.0	2.9 ± 0.9	<0.001
HDL-C (mmol/L)	1.5 ± 0.5	1.4 ± 0.5	<0.001	1.4 ± 0.6	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.6	<0.001
Triglycerides (mmol/L)	1.1 (0.8-1.5)	1.4 (1.0-2.1)	<0.001	1.6 (1.1-2.4)	1.5 (1.0-2.2)	1.4 (1.0-2.0)	1.3 (0.9-1.8)	<0.001
hs-CRP (mg/L)	0.9 (0.4-2.0)	1.3 (0.6-2.9)	<0.001	1.2 (0.6-2.6)	1.3 (0.7-2.7)	1.4 (0.6-2.9)	1.6 (0.7-3.5)	<0.001
Uric acid (μmol/L)	281.1 ± 79.2	308.8 ± 87.8	<0.001	318.4 ± 96.7	301.2 ± 87.3	306.4 ± 82.2	316.3 ± 85.0	<0.001
eGFR (mL/min/1.73m^2)	88.8 ± 19.2	87.9 ± 19.6	<0.001	99.1 ± 20.5	90.2 ± 18.5	84.4 ± 16.7	74.9 ± 16.0	<0.001
ALT (U/L)	17.0 (12.0-23.0)	19.0 (14.0-26.0)	<0.001	22.0 (16.0-30.0)	19.0 (14.0-26.0)	19.0 (14.0-25.0)	17.0 (13.0-22.0)	<0.001
Smoking status			<0.001					<0.001
Never	14,655 (59.2)	14,190 (57.3)		2,506 (47.7)	4,182 (52.1)	4,715 (62.4)	2,787 (70.8)	
Former smoker	853 (3.4)	1,008 (4.1)		220 (4.2)	307 (3.8)	303 (4.0)	178 (4.5)	
Current smoker	8,579 (34.6)	8,874 (35.8)		2,463 (46.9)	3,410 (42.5)	2,262 (30.0)	739 (18.8)	
Alcohol intake status			<0.001					<0.001
Never	15,723 (63.5)	14,756 (59.6)		2,336 (44.5)	4,380 (54.6)	5,105 (67.6)	2,935 (74.5)	
Former	362 (1.5)	408 (1.6)		73 (1.4)	146 (1.8)	122 (1.6)	67 (1.7)	
Light	6,155 (24.8)	6,530 (26.4)		2,191 (41.7)	2,313 (28.8)	1,476 (19.6)	450 (14.0)	
Moderate	1,179 (4.8)	1,431 (5.8)		340 (6.5)	498 (6.2)	443 (5.9)	150 (3.8)	
Heavy	1,133 (4.6)	1,469 (5.9)		300 (5.7)	658 (8.2)	366 (4.9)	145 (3.7)	
Physical activities			0.532					<0.001
No physical activity	5,547 (22.4)	5,414 (21.9)		1,376 (26.2)	2,020 (25.2)	1,314 (17.4)	704 (17.9)	
Occasional physical activity	12,582 (50.8)	12,636 (51.0)		2,924 (55.6)	4,155 (51.8)	3,758 (49.8)	1,799 (45.7)	
Regular physical activity	3,422 (13.8)	3,467 (14.0)		469 (8.9)	923 (11.5)	1,367 (18.1)	708 (18.0)	
Sodium intake			<0.001					<0.001
Low intake	3,178 (12.8)	2,963 (12.0)		694 (13.2)	1,038 (12.9)	805 (10.7)	426 (10.8)	
Moderate intake	15,701 (63.4)	15,486 (62.5)		3,269 (62.2)	5,066 (63.1)	4,791 (63.4)	2,360 (59.9)	
High intake	1,932 (7.8)	2,337 (9.4)		629 (12.0)	824 (10.3)	615 (8.1)	269 (6.8)	
High school or beyond, yes	1,850 (7.5)	2,034 (8.2)	<0.001	1,237 (23.5)	424 (5.3)	222 (2.9)	151 (3.8)	<0.001
Antihypertensive medications	1,659 (6.7)	2,627 (10.6)	<0.001	235 (4.5)	791 (9.9)	981 (13.0)	620 (15.7)	<0.001
Antidiabetic medications	376 (1.5)	576 (2.3)	<0.001	30 (0.6)	157 (2.0)	235 (3.1)	154 (3.9)	<0.001
Antihyperlipidemic medications	120 (0.5)	231 (0.9)	<0.001	37 (0.7)	79 (1.0)	70 (0.9)	45 (1.1)	0.1656
Hypertension [b]	2,101 (8.5)	3,289 (13.3)	<0.001	318 (6.1)	1,024 (12.8)	1,212 (16.0)	735 (18.7)	<0.001
Diabetes [c]	610 (2.5)	858 (3.5)	<0.001	44 (0.8)	235 (2.9)	346 (4.6)	233 (5.9)	<0.001
Hepatitis B (+)	958 (3.9)	766 (3.1)	<0.001	214 (4.1)	269 (3.3)	208 (2.8)	75 (1.9)	<0.001

Continuous variables were presented as mean ± standard deviation (SD) or median (25th-75th percentiles), while categorical variables were presented as N (percentage). [a] *P* values were derived from Student's t-tests or Mann-Whitney U tests for continuous variables according to the data distribution, and Chi-square tests or Fisher's exact test for the categorical variables. [b] Hypertension was defined if SBP ≥140 mmHg or DBP ≥90 mmHg during measurement, or if the participant self-reported physician diagnosis, or use of antihypertensive medications. [c] Diabetes was defined if the fasting glucose level was ≥7.0 mmol/L, or the participant self-reported physician diagnosis, or use of antidiabetic medications (insulin or oral hypoglycemic agents). Hepatitis B was defined if the participant's HBsAg was positive. Abbreviations: MAFLD, metabolic dysfunction–associated fatty liver disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen.

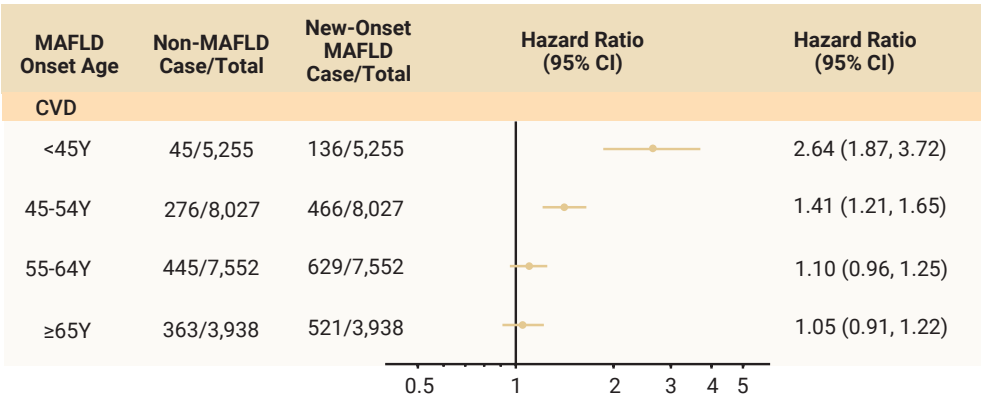


Figure 1. Forest plot of the hazard ratios (95% confidence interval) for incident cardiovascular disease among the new-onset MAFLD participants across age groups (N = 49,544) The models were adjusted for heart rate, uric acid, eGFR, ALT, smoking status, alcohol consumption, physical activity, sodium intake, and education level. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; MAFLD, metabolic dysfunction–associated fatty liver disease.

Adverse cardiovascular disease outcomes

The incident CVD risk of MAFLD stratified by the MAFLD onset age is shown in Figure 1. During an average follow-up of 8.27 years, we identified 2,881 cases of CVD (including 568 cases of MI, 2,110 cases of IS, and 352 cases of HS, with 58 overlap cases for MI and stroke, and 91 overlap cases for IS and HS). After multivariate adjustment, the risk of CVD was generally higher in the new-onset MAFLD population than in the non-MAFLD population across the age range. Interestingly, the risk estimates gradually declined with each decade of increase in the MAFLD onset age. MAFLD patients whose onset age was younger than 45 years had the highest CVD risk among all age groups (HR, 2.64 [1.87-3.72]). For the age groups of 45 to 54 years, the HR (95% CI) for CVD was 1.41 (1.21-1.65). However, the HR (95% CI) for CVD was not statistically significant in the age groups of 55 to 64 and older than 65 years groups (HR, 1.10 [0.96-1.25] and 1.05 [0.91-1.22], respectively).

Subgroup analysis of cardiovascular diseases

Similar results were obtained for stroke and IS in the subtype analyses (Figure 2). MAFLD cases whose onset age was younger than 45 years had the highest risk in all age groups with an HR (95% CI) of 3.16 (2.13-4.69) for stroke and 3.76 (2.41-5.86) for IS. For the participants with onset age of 45 to 54 years, the HR (95% CI) was 1.40 (1.18-1.66) for stroke and 1.48 (1.23-1.77) for IS. However, the HRs (95% CI) for stroke and IS were not statistically significant in the age groups of 55 to 64 and older than 65 years groups. It is worth noting that almost all HRs (95% CI) in MI and HS were not statistically significant, which could be limited by the relatively small sample size of the cases. Nevertheless, we still observed a higher MI risk among the relatively early-onset MAFLD group (45 to 54 years) compared with the onset groups older than 55 years.

Sensitivity analysis

The findings were generally similar to the primary analysis in sensitivity analyses excluding current drinkers (N = 31,647) (Table S1), analyses excluding participants with hepatitis B, cirrhosis, and cancer (N = 45,976) (Table S2), analyses with Fine-Gray models to account for the competing risk of mortality (N = 49,544) (Figure S5), analyses using weighted Cox proportional hazards regression models (N = 49,544) (Table S4), and analyses excluding the CVD outcome events occurring within the first year of the follow-up (N = 49,072) (Table S5). The findings did not materially change among the analyses of new-onset MAFLD patients with non-fatal CVD (N = 48,828) or fatal CVD (N = 46,756) (Figures S6-S7) and analyses of NAFLD patients across age groups (N = 34,624) (Figures S8-S9). The finding also did not substantially differ among subgroup analyses by sex among new-onset MAFLD patients (N = 49,544) (Table S6). A similar trend was observed among those male patients with new-onset MAFLD. It is worth noting that almost all HRs (95% CI) in MI, stroke, IS and HS were not statistically significant in females, which could be limited by the relatively small sample size of cases. In addition, the observed associations did not materially change in analyses with additional adjustment for the use of medication (antidiabetic, antihypertensive, or antihyperlipidemic) (N = 49,544) (Figures S3-S4) and analyses excluding participants with the use of medications (antidiabetic, antihypertensive, or antihyperlipidemic) (N = 44,478) (Table S3).

Figure S10 illustrated the dose-response relations between age at MAFLD diagnosis and the risk of CVD. We found that the early-onset participants (defined as diagnosis at <45 years) had a higher risk of incident CVD compared to other MAFLD onset-age groups.

DISCUSSION

In this large community-based cohort study in China, we observed that CVD risk gradually declined with each decade increase in MAFLD onset age. Notably, the highest incidence of CVD risk was observed in participants with early-onset MAFLD (onset age <45 years). This study provides a novel insight that the MAFLD onset age is an important risk stratification in the prevention, screening, and management of future CVD risk.

Systematic reviews have summarized that NAFLD was strongly associated with an increased risk of CVD.[35,36] However, given that MAFLD is a new definition updated from NAFLD and combined liver fatty lesions and metabolic abnormalities, there is a lack of studies to assess the association between MAFLD and CVD risk. In line with our findings, a cohort study of nearly 9 million middle-aged Korean adults found that MAFLD was associated with a significantly higher risk of incident CVD events, including MI, IS, heart failure, or CVD-related death after a 10-year follow-up.[37] Furthermore, a liver biopsy study reported that patients with NAFLD or MAFLD had intermediate or high cardiovascular risk (defined by atherogenic ratios; the risks were 25.7% and 36.4%, respectively, for NAFLD and MAFLD) and a higher incidence of CVD (12.8% and 20.1%, respectively).[38] A systematic meta-analysis of 22 studies involving 379,801 patients also summarized that MAFLD patients were more likely to have cardiovascular risk factors, including hypertension (OR, 1.17 [1.07-1.29]; $P = 0.0007$) and diabetes (OR, 1.09 [1.00-1.19]; $P = 0.0420$).[39] Given that CVD remains a leading cause of death and disease burden both globally,[11,40] even a modest increase in CVD risk would translate into a large burden of excess morbidity and mortality. Nevertheless, the current guidelines do not consider MAFLD onset age as an important risk stratifier of CVD.[1,4] The patients with MAFLD have the hepatic manifestation of a multisystem disorder.[2] The liver injury in these patients would independently contribute to the pathogenesis of CVD.[25] So far, few studies have had sufficient support to investigate MAFLD diagnosis across the entire age range, which is important for early prevention and identification of susceptible individuals with CVD throughout the lifespan.

However, the mechanisms underlying this observed association remain unknown. Several plausible interpretations are proposed. First, early-onset MAFLD patients had a longer MAFLD duration than later-onset MAFLD patients. An international multidisciplinary consensus statement on MAFLD and CVD risk indicates that MAFLD and CVD share multiple cardiometabolic risk factors, including systemic low-grade inflammation, endothelial dysfunction, increased oxidative stress, insulin resistance, and an atherogenic lipoprotein profile.[41] Therefore, early-onset MAFLD cases may have a longer duration of CVD risk factors, which may provide a pathological basis for CVD development. Specifically, several pathophysiological mechanisms that may promote the development of CVD in patients with MAFLD include activation of the renin-angiotensin system,[42] some shared genetic polymorphisms (e.g., *PNPLA3 I148M*, and *TM6SF2 E167K*),[43,44] and dysregulated gut microbiota.[45,46] Second, compared with late-onset MAFLD patients, most early-onset patients tend to ignore their current health problems and are especially unlikely to be aware of their future heightened cardiometabolic risk,[47] which would subsequently translate into a great CVD burden. Thus, given that current strategies[48] mainly emphasize MAFLD treatment in middle-aged and elderly individuals while overlooking the significant cardiometabolic risks of

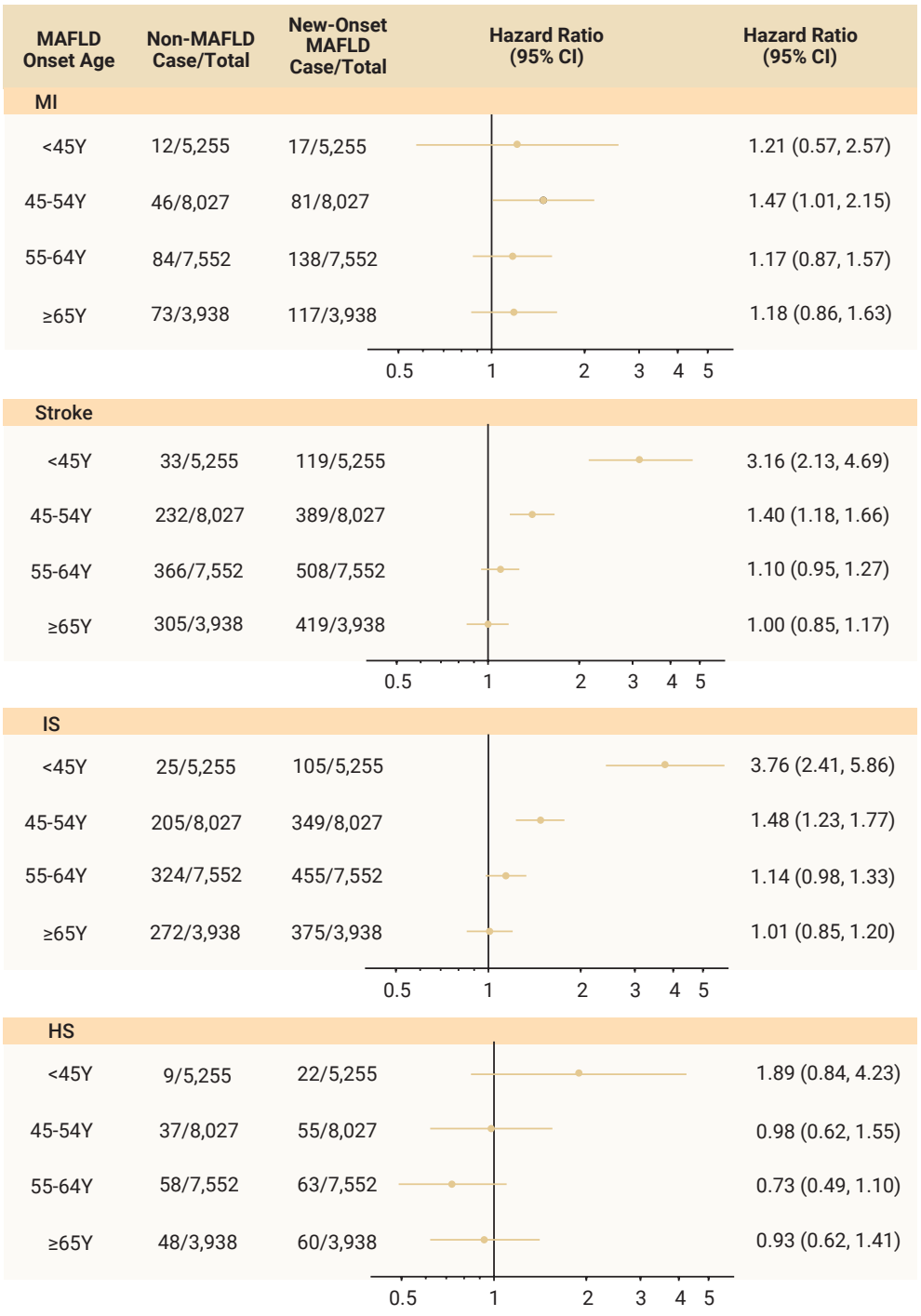


Figure 2. Forest plot of the hazard ratios (95% confidence interval) of the subtypes of cardiovascular disease of the new-onset MAFLD participants across age groups (N = 49,544) The models were adjusted for heart rate, uric acid, eGFR, ALT, smoking status, alcohol consumption, physical activity, sodium intake, and education level. Abbreviations: CI, confidence interval; MAFLD, metabolic dysfunction–associated fatty liver disease; MI, myocardial infarction; IS, ischemic stroke; HS, hemorrhagic stroke.

early-onset MAFLD in young people, our research findings will provide critical information for policy development. By contrast, we did not observe a significant association between late-onset MAFLD (defined as diagnosis at >55 years) and the risk of incident CVD. A potential explanation includes that MAFLD patients, by definition,[1,2] may have fatty liver lesions, obesity, type 2 diabetes, hypertension, and dyslipidemia, which are also risk factors for CVD. Therefore, the participants who were diagnosed with MAFLD at an older age, have a shorter duration of liver injury and metabolic abnormalities, which may have a lower CVD risk compared with younger people with MAFLD. Furthermore, compared with older people, young people tended to adhere to unhealthy lifestyles (e.g., long duration of sedentary behavior, high-calorie diets, etc.),[2,10] which would accelerate the development of CVD. Further large cohort studies are warranted to evaluate the association between late-onset MAFLD and the risk of incident CVD to confirm these findings and verify the biological pathways.

Our study had several strengths. To our knowledge, this study is the first prospective study to evaluate the association of early-onset MAFLD with incident CVD risk during an average follow-up duration of 8.27 years. To minimize the impact of confounding factors, we randomly selected a control group without MAFLD in the same year, matched for age (±1 year) and sex. In addition, the major strengths include the large sample size, prospective design, comprehensive coverage of electronic health data, and biennial follow-up with good data quality.

However, some limitations of this study need to be acknowledged. First, the hepatic steatosis was explored through abdominal ultrasound examination in our study. A liver biopsy is the gold standard for diagnosing fatty liver.[49] Even though, ultrasound examination is the most widely used and cost-effective non-invasive diagnostic method.[8] A meta-analysis showed that compared with histology, the overall sensitivity and specificity of ultrasound in detecting moderate to severe fatty liver were 84.8% (95% CI: 79.5-88.9) and 93.6% (95% CI: 87.2-97.0), respectively,[50] which showed fair reliability of ultrasonography for the detection of fatty liver. Furthermore, international guidelines have recognized the role of ultrasound examination in large epidemiological studies.[2] Second, the data of the homeostasis model assessment-insulin resistance score was not available in our study. Some MAFLD cases may be missed and the risk of CVD may be underestimated. Third, we defined the age of onset of MAFLD as the date of examination when the patient was first diagnosed with MAFLD minus the patient's birth date. The estimated age of onset may not be accurate for all individuals. Nevertheless, we objectively diagnosed the new-onset MAFLD cases with the biennial follow-up, which enabled us to minimize the potential bias (within two years). Moreover, we categorized the MAFLD onset age group into 10-year intervals, which may lead to less influence on the classification of the onset age group. In addition, we acknowledge that the true onset date could be any time between follow-up visits and that there is a measurement error in this estimation, but we deemed that this type of measurement error could be random, and the proportion of subsequent misclassification into different age groups would be small and would not substantially affect our results. Fourth, the aspartate aminotransferase (AST) levels were not measured in our study. Therefore, we were unable to calculate the non-invasive liver fibrosis score to assess the severity of MAFLD. Finally, all participants were employees and retirees of the Kailuan community in China, with a high proportion of male participants. Therefore, the generalizability of our findings should be tested in other demographic, racial, and ethnic populations.

Our findings address the importance of intensive prevention strategies for CVD and adequate therapy in young MAFLD patients. The rates of MAFLD

awareness, treatment, and control are relatively low among young adults,[51] and current guidelines do not include the onset age of MAFLD in the prevention and early identification of CVD.[4] Future guideline iterations may add revisions that denote management approaches for early-onset MAFLD patients.

REFERENCES

1. Eslam, M., Sanyal, A.J., and George, J. (2020). MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology **158**: 1999–2014.e1991. DOI: 10.1053/j.gastro.2019.11.312.
2. Eslam, M., Newsome, P.N., Sarin, S.K., et al. (2020). A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J. Hepatol. **73**: 202–209. DOI: 10.1016/j.jhep.2020.03.039.
3. Shiha, G., Korenjak, M., Eskridge, W., et al. (2021). Redefining fatty liver disease: An international patient perspective. Lancet Gastroenterol. Hepatol. **6**: 73–79. DOI: 10.1016/S2468-1253(20)30294-6.
4. Eslam, M., Sarin, S.K., Wong, V.W., et al. (2020). The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol. Int. **14**: 889–919. DOI: 10.1007/s12072-020-10094-2.
5. Eslam, M., and George, J. (2021). MAFLD: A game changer redefining fatty liver disease for adults and children. J. Hepatol. **74**: 992–994. DOI: 10.1016/j.jhep.2021.01.004.
6. Spearman, C.W., Desalegn, H., Ocama, P., et al. (2021). The sub-Saharan Africa position statement on the redefinition of fatty liver disease: From NAFLD to MAFLD. J. Hepatol. **74**: 1256–1258. DOI: 10.1016/j.jhep.2021.01.015.
7. Mendez, S.N., Arrese, M., Gadano, A., et al. (2021). The Latin American Association for the Study of the Liver (ALEH) position statement on the redefinition of fatty liver disease. Lancet Gastroenterol. Hepatol. **6**: 65–72. DOI: 10.1016/S2468-1253(20)30340-X.
8. Liu, J., Ayada, I., Zhang, X., et al. (2022). Estimating global prevalence of metabolic dysfunction-associated fatty liver disease in overweight or obese adults. Clin. Gastroenterol. Hepatol. **20**: e573–e582. DOI: 10.1016/j.cgh.2021.02.030.
9. Lim, S., Kim, J.W., and Targher, G. (2021). Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. Trends Endocrinol. Metab. **32**: 500–514. DOI: 10.1016/j.tem.2021.04.008.
10. Doycheva, I., Watt, K.D., and Alkhouri, N. (2017). Nonalcoholic fatty liver disease in adolescents and young adults: The next frontier in the epidemic. Hepatology **65**: 2100–2109. DOI: 10.1002/hep.29068.
11. Roth, G.A., Mensah, G.A., Johnson, C.O., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. J. Am. Coll. Cardiol. **76**: 2982–3021. DOI: 10.1016/j.jacc.2020.11.010.
12. GBD 2017 DALYs and HALE Collaborators. (2018). Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet **392**: 1859-1922. DOI: 10.1016/s0140-6736(18)32335-3.
13. Andersson, C., and Vasan, R.S. (2018). Epidemiology of cardiovascular disease in young individuals. Nat. Rev. Cardiol. **15**: 230–240. DOI: 10.1038/nrcardio.2017.154.
14. Strong, J.P., Malcom, G.T., McMahan, C.A., et al. (1999). Prevalence and extent of atherosclerosis in adolescents and young adults: Implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA **281**: 727–735. DOI: 10.1001/jama.281.8.727.
15. Piepoli, M.F., Hoes, A.W., Agewall, S., et al. (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur. Heart J. **37**: 2315–2381. DOI: 10.1093/eurheartj/ehw106.
16. Murthy, V.L., Reis, J.P., Pico, A.R., et al. (2020). Comprehensive metabolic phenotyping refines cardiovascular risk in young adults. Circulation **142**: 2110–2127. DOI: 10.1161/circulationaha.120.047689.
17. Gooding, H.C., Ning, H., Gillman, M.W., et al. (2017). Application of a lifestyle-based tool to estimate premature cardiovascular disease events in young adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. JAMA Intern. Med. **177**: 1354–1360. DOI: 10.1001/jamainternmed.2017.2922.
18. Gidding, S.S., and Robinson, J. (2019). It is now time to focus on risk before age 40. J. Am. Coll. Cardiol. **74**: 342–345. DOI: 10.1016/j.jacc.2019.04.064.
19. Wang, C., Yuan, Y., Zheng, M., et al. (2020). Association of age of onset of hypertension with cardiovascular diseases and mortality. J. Am. Coll. Cardiol. **75**: 2921–2930. DOI: 10.1016/j.jacc.2020.04.038.
20. Sattar, N., Rawshani, A., Franzén, S., et al. (2019). Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. Circulation **139**: 2228–2237. DOI: 10.1161/circulationaha.118.037885.
21. Zhao, M., Song, L., Sun, L., et al. (2021). Associations of type 2 diabetes onset age with cardiovascular disease and mortality: The kailuan study. Diabetes Care **44**: 1426–1432. DOI: 10.2337/dc20-2375.
22. Rawshani, A., Sattar, N., Franzén, S., et al. (2018). Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet **392**: 477–486. DOI: 10.1016/s0140-6736(18)31506-x.
23. Li, L., Zhao, M., Wang, C., et al. (2021). Early onset of hyperuricemia is associated with increased cardiovascular disease and mortality risk. Clin. Res. Cardiol. **110**: 1096–1105. DOI: 10.1007/s00392-021-01849-4.
24. Huang, Z., Wang, X., Ding, X., et al. (2022). Association of age of metabolic syndrome onset with cardiovascular diseases: The kailuan study. Front. Endocrinol. **13**: 857985. DOI: 10.3389/fendo.2022.857985.
25. Armandi, A., and Bugianesi, E. (2023). Extrahepatic outcomes of nonalcoholic fatty liver disease: Cardiovascular diseases. Clin. Liver Dis. **27**: 239–250. DOI: 10.1016/j.cld.2023.01.018.
26. Wu, Z., Jin, C., Vaidya, A., et al. (2016). Longitudinal patterns of blood pressure, incident cardiovascular events, and all-cause mortality in normotensive diabetic people. Hypertension **68**: 71–77. DOI: 10.1161/hypertensionaha.116.07381.
27. Jin, C., Chen, S., Vaidya, A., et al. (2017). Longitudinal change in fasting blood glucose and myocardial infarction risk in a population without diabetes. Diabetes Care **40**: 1565–1572. DOI: 10.2337/dc17-0610.
28. Li, W., Jin, C., Vaidya, A., et al. (2017). Blood pressure trajectories and the risk of intracerebral hemorrhage and cerebral infarction: A prospective study. Hypertension **70**: 508–514. DOI: 10.1161/HYPERTENSIONAHA.117.09479.
29. Tunstall-Pedoe, H., Kuulasmaa, K., Amouyel, P., et al. (1994). Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation **90**: 583-612. DOI: 10.1161/01.cir.90.1.583.
30. Thygesen, K., Alpert, J.S., Jaffe, A.S., et al. (2018). Fourth universal definition of myocardial infarction (2018). Circulation **138**: e618–e651. DOI: 10.1161/cir.0000000000000617.
31. WHO. (1989). Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke **20**: 1407-1431. DOI: 10.1161/01.str.20.10.1407.
32. Wang, Z.Y., Chen, S.H., Zhao, X.Y., et al. (2020). Application of Cox and extended regression models on modeling the effect of time-updated exposures in cohort studies. Zhonghua liu xing bing xue za zhi **41**: 957–961. DOI: 10.3760/cma.j.cn112338-20200119-00046.
33. Canchola, A.J., Stewart, S.L., Bernstein, L., et al. (2003). 1 COX REGRESSION USING DIFFERENT TIME-SCALES. Western Users of SAS Software. San Francisco, California. https://www.lexjansen.com/wuss/2003/DataAnalysis/i-cox_time_scales.pdf.
34. Schemper, M., Wakounig, S., and Heinze, G. (2009). The estimation of average hazard ratios by weighted Cox regression. Stat. Med. **28**: 2473–2489. DOI: 10.1002/sim.3623.
35. Mantovani, A., Csermely, A., Petracca, G., et al. (2021). Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol. Hepatol. **6**: 903–913. DOI: 10.1016/S2468-1253(21)00308-3.
36. Targher, G., Byrne, C.D., Lonardo, A., et al. (2016). Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J. Hepatol. **65**: 589–600. DOI: 10.1016/j.jhep.2016.05.013.
37. Lee, H., Lee, Y.H., Kim, S.U., et al. (2021). Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: A nationwide cohort study. Clin. Gastroenterol. Hepatol. **19**: 2138–2147.e2110. DOI: 10.1016/j.cgh.2020.12.022.
38. Guerreiro, G.T.S., Longo, L., Fonseca, M.A., et al. (2021). Does the risk of cardiovascular events differ between biopsy-proven NAFLD and MAFLD. Hepatol. Int. **15**: 380–391. DOI: 10.1007/s12072-021-10157-y.
39. Lim, G.E.H., Tang, A., Ng, C.H., et al. (2021). An observational data meta-analysis on the differences in prevalence and risk factors between MAFLD vs NAFLD. Clin. Gastroenterol. Hepatol. **21**: 619–629. DOI: 10.1016/j.cgh.2021.11.038.
40. Roth, G.A., Mensah, G.A., and Fuster, V. (2020). The global burden of cardiovascular diseases and risks: A compass for global action. J. Am. Coll. Cardiol. **76**: 2980–2981. DOI: 10.1016/j.jacc.2020.11.021.
41. Zhou, X.D., Targher, G., Byrne, C.D., et al. (2023). An international multidisciplinary consensus statement on MAFLD and the risk of CVD. Hepatol. Int. **17**: 773–791. DOI: 10.1007/s12072-023-10543-8.
42. Goh, G.B., Pagadala, M.R., Dasarathy, J., et al. (2015). Renin-angiotensin system and fibrosis in non-alcoholic fatty liver disease. Liver Int. **35**: 979–985. DOI: 10.1111/liv.12611.
43. Chew, N.W.S., Chong, B., Ng, C.H., et al. (2022). The genetic interactions between non-alcoholic fatty liver disease and cardiovascular diseases. Front. Genet. **13**: 971484. DOI: 10.3389/fgene.2022.971484.
44. Simons, N., Isaacs, A., Koek, G.H., et al. (2017). PNPLA3, TM6SF2, and MBOAT7 genotypes and coronary artery disease. Gastroenterology **152**: 912–913. DOI: 10.1053/j.gastro.2016.12.020.
45. Albillos, A., de Gottardi, A., and Rescigno, M. (2020). The gut-liver axis in liver disease: Pathophysiological basis for therapy. J. Hepatol. **72**: 558–577. DOI: 10.1016/j.jhep.2019.10.003.
46. Hu, H., Lin, A., Kong, M., et al. (2020). Intestinal microbiome and NAFLD: Molecular insights and therapeutic perspectives. J. Gastroenterol. **55**: 142–158. DOI: 10.1007/s00535-019-01649-8.
47. Bucholz, E.M., Gooding, H.C., and de Ferranti, S.D. (2018). Awareness of cardiovascular risk factors in U.S. young adults aged 18-39 years. Am. J. Prev. Med. **54**: e67-e77. DOI: 10.1016/j.amepre.2018.01.022.

48. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO). (2016). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J. Hepatol. 64: 1388–1402. DOI: 10.1016/j.jhep.2015.11.004.
49. Castera, L., Friedrich-Rust, M., and Loomba, R. (2019). Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 156: 1264–1281.e1264. DOI: 10.1053/j.gastro.2018.12.036.
50. Hernaez, R., Lazo, M., Bonekamp, S., et al. (2011). Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis. Hepatology 54: 1082–1090. DOI: 10.1002/hep.24452.
51. Lazarus, J.V., Mark, H.E., Anstee, Q.M., et al. (2022). Advancing the global public health agenda for NAFLD: A consensus statement. Nat. Rev. Gastroenterol. Hepatol. 19: 60–78. DOI: 10.1038/s41575-021-00523-4.

FUNDING AND ACKNOWLEDGMENTS

We are grateful to all the participants of the Kailuan Study. This study was supported by the National Key Research and Development Program of China (2022YFE0209900), the National Natural Science Foundation of China (82003428), and the Fundamental Research Funds for the Central Universities, HUST (2021XXJS019). Fundings had no role in the design, data analyses, or results interpretation of this study. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

MZ, SW, and Y. Yuan designed the study. MZ and SC collected and preprocessed the data of the Kailuan study. MZ and XW conducted the statistical analyses and drafted the manuscript. Y. Yin and CG contributed to revising the manuscript. SW and Y. Yuan contributed to the interpretation of the results and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

The study was conducted with the guidelines of the Declaration of Helsinki and approved by the Kailuan General Hospital Ethics Committee ([2006] Yi Lun Zi 5 Hao). All participants agreed to participate in the study and provided written informed consent.

DATA AND CODE AVAILABILITY

This study was based on the Kailuan cohort, an ongoing prospective cohort study conducted in Tangshan City, China. The detailed study design and procedures have been described elsewhere. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2024.100064

LEAD CONTACT WEBSITE

http://faculty.hust.edu.cn/yuanyu11/zh_CN/more/2349710/shjzgd/index.htm