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Metabolic Dysfunction-Associated Steatotic Liver Disease Is Associated With Accelerated Brain Ageing: A Population-Based Study

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is linked to cognitive decline and dementia risk. We aimed to investigate the association between MASLD and brain ageing and explore the role of low-grade inflammation.

Methods: Within the UK Biobank, 30 386 chronic neurological disorders-free participants who underwent brain magnetic resonance imaging (MRI) scans were included. Individuals were categorised into no MASLD/related SLD and MASLD/related SLD (including subtypes of MASLD, MASLD with increased alcohol intake [MetALD] and MASLD with other combined aetiology). Brain age was estimated using machine learning by 1079 brain MRI phenotypes. Brain age gap (BAG) was calculated as the difference between brain age and chronological age. Low-grade inflammation (INFLA) was calculated based on white blood cell count, platelet, neutrophil granulocyte to lymphocyte ratio and C-reactive protein. Data were analysed using linear regression and structural equation models.

Results: At baseline, 7360 (24.2%) participants had MASLD/related SLD. Compared to participants with no MASLD/related SLD, those with MASLD/related SLD had significantly larger BAG ($\beta = 0.86$, 95% CI = 0.70, 1.02), as well as those with MASLD ($\beta = 0.59$, 95% CI = 0.41, 0.77) or MetALD ($\beta = 1.57$, 95% CI = 1.31, 1.83). The association between MASLD/related SLD and larger

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BAG was significant across middle-aged (< 60) and older (≥ 60) adults, males and females, and *APOE* ε4 carriers and non-carriers. INFLA mediated 13.53% of the association between MASLD/related SLD and larger BAG ($p < 0.001$).
Conclusion: MASLD/related SLD, as well as MASLD and MetALD, is associated with accelerated brain ageing, even among middle-aged adults and *APOE* ε4 non-carriers. Low-grade systemic inflammation may partially mediate this association.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), defined as the presence of steatotic liver disease (SLD) and one or more cardiometabolic risk factors, has emerged as the most common chronic liver condition, affecting more than one-third of the world's adult population [1]. Globally, the prevalence of MASLD has increased from 25.3% (1990–2006) to 38.2% (2016–2019) and is still growing rapidly, with an annual incidence rate of 4.9% [2, 3]. Thus far, accumulating evidence has shown that people with MASLD are at an increased risk of cognitive impairment and dementia [4, 5].

In recent years, multimodal brain magnetic resonance imaging (MRI) and machine learning have been applied to brain age modelling to provide a comprehensive perspective of an individual's brain ageing by integrating cerebral functional and structural metrics [6]. The brain age gap (BAG) is the difference between predicted brain age and chronological age. A larger BAG indicates a deviation from the normal ageing process (i.e., accelerated brain ageing) and is associated with subsequent cognitive decline and dementia [7]. Identifying accelerated brain ageing and related risk factors can inform early intervention for brain health in the preclinical stage.

Recent neuroimaging evidence suggests that non-alcoholic fatty liver disease (NAFLD)/metabolic dysfunction-associated fatty liver disease (MAFLD) is associated with global brain atrophy [8, 9], hippocampal atrophy [10], cortical thickness reduction [11] and increased small-vessel disease burden [12–14], but findings have been inconsistent [8, 9]. This evidence suggests the existence of the 'liver-brain' axis. However, the association between NAFLD/MAFLD, in particular MASLD, and brain age has not been explored to date. Moreover, MASLD is considered not only a hepatic but also a systemic inflammatory disease [15], and inflammation is an important mechanism underlying brain ageing [16]. However, to the best of our knowledge, no studies have yet examined whether inflammation could act as a mediator in the effects of MASLD on brain ageing.

To fill these knowledge gaps, we conducted a comprehensive examination of the association between MASLD and brain ageing in over 30000 middle-aged and older adults, utilising detailed neuroimaging data from the UK Biobank covering six different MRI modalities. Specifically, (1) we examined the association of MASLD/related SLD and its subtypes (MASLD, MetALD and MASLD with other combined aetiology) with BAG; (2) compared the effects of NAFLD, MAFLD and MASLD on BAG; and (3) investigated the mediating effects of low-grade systemic inflammation on the MASLD-BAG association.

2 | Methods

2.1 | Study Design, Setting and Participants

We used a large-scale population-based cohort study, the UK Biobank, of 502353 UK residents aged 37–73 years [17]. A comprehensive physical measurement and clinical evaluation were performed on the enrolled subjects at baseline starting in 2006. Then, a sub-sample of 42806 participants underwent neuroimaging assessment between 2014 and 2020. Of these, 34296 participants with complete brain MRI data were included in the brain age construct, as illustrated in Figure 1.

After further excluding 3910 participants with prevalent chronic brain disorders at MRI assessment ($n = 1459$; see Table S1), severe liver disease or acute hepatitis ($n = 195$), or missing variables to define fatty liver disease ($n = 2288$), 30386 participants were entered into the MASLD-brain age analysis (Figure 1).

2.2 | Assessment of Metabolic Dysfunction-Associated Steatotic Liver Disease

The fatty liver index (FLI) was calculated based on body mass index (BMI), waist circumference, triglycerides and gamma-glutamyltransferase. It has been proven to be a reliable alternative to imaging techniques, such as ultrasound and transient elastography, demonstrating good diagnostic performance [18]. SLD was defined as a FLI ≥ 60 [19]. MASLD was defined as the presence of SLD with one or more cardiometabolic risk factors. Individuals with increased or excessive alcohol intake (weekly intake ≥ 210 g (males) or ≥ 140 g (females); Method S1) or those with concurrent liver disease (ICD-10 codes, B15-B19, K70, K71, K74.3-K74.5, K75.4, E83.0, E83.1) were excluded from the MASLD [20]. The assessment of key variables used in the MASLD definition is shown in Method S2 and Table S2. NAFLD and MAFLD were defined by previous studies [21].

2.2.1 | Subtypes of MASLD/related SLD

Individuals with a combination of MASLD and increased alcohol intake (210–420 g per week for men or 140–350 g per week for women) were classified as having MASLD with increased alcohol intake (MetALD). Individuals with MASLD and liver disease, but without increased or excessive alcohol intake, were classified as having MASLD with other combined aetiology (abbreviated as 'other' in subsequent text). MASLD, MetALD and other MASLD were collectively referred to as 'MASLD/related SLD'.

Summary

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with accelerated brain ageing even in middle-aged adults and *APOE* ε4 non-carriers.
- Low-grade inflammation mediated the association between MASLD and brain ageing.
- Our findings highlight MASLD as an ideal target for anti-inflammatory-based interventions to promote brain health.

2.3 | MRI Data Acquisition and Pre-Processing

Details of the image acquisition and processing are available on the UK Biobank website in the brain scan protocol and brain imaging documentation [22, 23]. Briefly, participants were scanned with a Siemens Skyra 3T scanner with a standard Siemens 32-channel head coil, including T1-weighted imaging, T2 FLAIR imaging, susceptibility-weighted structural imaging and task and resting-state fMRI. In addition, diffusion imaging (DTI) was applied by an echo plane, single-shot Stejskal-Tanner pulse sequence in 50 distinct diffusion-weighted directions. The specific parameters of the neuroimaging are summarised in Table S5. T1-weighted imaging provides volumetric and morphological information on brain tissue. T2-FLAIR traps signal attenuation arising from the interaction between water molecules and is mainly used for the detection of pathologies such as white matter lesions. T2* (or susceptibility-weighted imaging) is sensitive to magnetic cerebral components and is used to detect venous vessels, microbleeds, iron and calcium. Resting-state and task fMRI measure blood oxygen level-dependent signal fluctuations when subjects are at rest and performing a task or experiencing sensory stimuli (face/shape matching task), respectively, providing information on the amplitude of fluctuations in spontaneous activity within brain regions or functional connectivity between different regions. DTI measures the movement of water molecules in their local tissue and assesses the microstructural integrity of white matter [24].

Summary measurements of image-derived phenotypes (IDPs) were generated by an image processing pipeline developed by the UK Biobank using publicly available image processing tools FSL (FMRIB Software Library, version 5.0.10, http://fsl.fmrib.ox.ac.uk/fsl) and FreeSurfer (version 6.0) [25]. Finally, 1079 neuroimaging phenotypes were generated, including T1-weighted = 165, T2-FLAIR = 1, SWI = 14, task fMRI = 14, resting-state fMRI = 210 and diffusion-MRI = 675. A full list of all 1079 IDPs is provided in Table S3. All MRI phenotypes were Z-transformed before modelling.

2.4 | Calculation of Machine Learning-Based Brain Age

Brain age was modelled based on multi-modalities neuroimaging phenotypes, as we previously published [26, 27]. A detailed description of the brain age calculation is available in Supporting

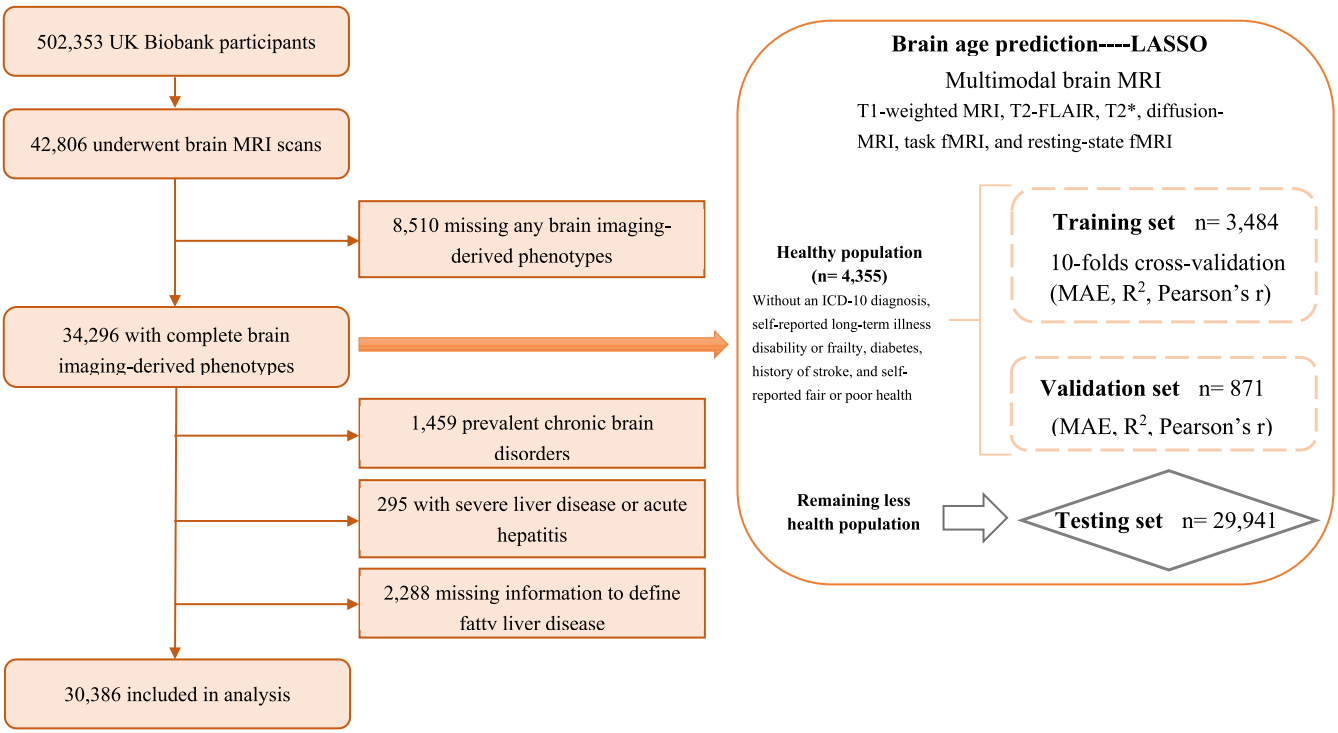

FIGURE 1 | Population selection flowchart. Among the brain age modelling subsample. Three subsets were defined, including a training set (for training the brain age model, $n = 3484$), a validation set (for validating model performance, $n = 871$) and a testing set ($n = 29\,941$). The training and testing data only included people who met health criteria at the time of the scan ($n = 4355$), thus excluding people with an ICD-10 diagnosis (field ID 41270), self-reported long-term illness disability or frailty (field ID 2188), diabetes (field ID 2443), history of stroke (field ID 4056) and self-reported fair or poor health status (field ID 2178).

Information S2, and the workflow is illustrated in Figure S1. Briefly, we combined three feature selection strategies (no feature selector, FeatureWiz and RFECV) with three machine learning models—Least Absolute Shrinkage and Selection Operator (LASSO) regression, eXtreme Gradient Boosting (XGBoost) and Support Vector Regression (SVR) [28] – to predict brain age (Tables S6 and S7). The criterion of minimum mean absolute error (MAE) was used to select the best-performing model and ultimately LASSO without feature selection was identified as the brain age prediction model (Tables S4 and S8). Moreover, as age bias is observed (Figure S2), we corrected the age bias in brain age prediction as the corrected brain age = (original brain age − β) / α (where coefficients α and β are the slope and intercept of the linear regression model used to estimate the brain age in the training set) [29].

BAG, the outcome of the current study, was defined as corrected brain age minus chronological age. A positive BAG means that the predicted brain age is higher than chronological age, that is accelerated brain ageing; a negative BAG means that the predicted brain age is lower, that is delayed brain ageing [7, 30].

2.5 | Assessment of Inflammation

Four recognised indicators of systemic inflammation were selected, including white blood cell count (WBC), platelet count, neutrophil count, C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR). Values less than Quartile (Q)1–3* Interquartile Quartile Rating (IQR) or greater than Q3 + 3* IQR were defined as extreme outliers and were eliminated before analysis [31]. A composite score for low-grade inflammation (INFLA) was calculated, incorporating CRP, WBC, platelet count and NLR, which act synergistically in pro-inflammatory effects in different biological processes [32]. Each inflammatory factor is divided into deciles, with scores of 1 to 4 on quartiles 7 to 10, scores of −4 to −1 on quartiles 1 to 4, and scores of 0 on quartiles 5 to 6. Then the final INFLA score was obtained by an equal-weighted sum of the four inflammatory factors. INFLA ranges from −16 to +16, with higher scores indicating higher levels of inflammation [32].

2.6 | Covariates

Demographic characteristics – age, sex (female or male), education (college or non-college; highest level of formal education attained) and race (white or non-white) – were collected through a computerised touchscreen questionnaire. Socioeconomic status was ascertained by the Townsend deprivation index (TDI) [33]. Smoking status was categorised as never, former or current smoker. Regular physical activity was defined as at least 150 min of moderate activity per week, 75 min of vigorous activity per week or an equivalent combination [34]. Social contact was evaluated based on responses to the question, 'How often do you visit friends or family or have them visit you?' Response options were as follows: Almost daily/2–4 times a week/about once a week/about once a month/once every few months/never or almost never/no friends/family outside household/do not know/prefer not to answer. These responses were further classified as regular or irregular according to a median [26]. The estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2012 formula based on creatinine and Cystatin C, taking into account age, race and sex [35]. Cardiovascular disease including myocardial infarction, angina, congestive heart failure and atrial fibrillation was assessed based on self-reported history and registered medical code [36]. Moreover, the *APOE* genes (rs429358 and rs7412) were genotyped and dichotomized as carriers versus non-carriers of the ε4 allele.

2.7 | Statistical Analysis

Baseline characteristics of the study population were presented as number (%) for categorical variables and mean ± standard deviation or median (P_{25}, P_{75}) for continuous variables. Alpha was set at 0.05 for all analyses. Statistical analyses were performed using Python (version 3.8.0 with sklearn) and Stata SE 16.0 (Stata Corp, College Station, Texas).

2.7.1 | Association between MASLD and BAG

The associations of MASLD/related SLD and its subtypes with BAG were analysed using linear regression models to estimate the β-coefficients and 95% confidence intervals (CIs). The basic models were adjusted for age, sex and education. Multivariable-adjusted models were further adjusted for race, TDI, BMI, smoking status, physical activity, social contact, cardiovascular disease, eGFR and *APOE* ε4. These covariates were selected based on current data availability and previous studies. Cardiometabolic risk factors (such as BMI, waist circumference, diabetes), alcohol consumption and concomitant liver disease were not included as covariates as they were already included in the definition of MASLD. In addition, we also analysed the association of NAFLD and MAFLD with BAG.

2.7.2 | Sensitivity Analysis

(1) Stratified analyses were performed to explore the consistency of the MASLD-BAG association among participants of different ages (< 60 vs. ≥ 60 years), sex (female vs. male), and *APOE* ε4 status (carriers vs. non-carriers). (2) The primary analysis was repeated by further adjusting for the use of lipid-lowering drugs. (3) To minimise the impact of MRI measurement error on the results, MRI head position and MRI assessment centre were added as additional covariates. (4) Rerun the MASLD-BAG association after excluding participants with increased or excessive alcohol intake or with concomitant liver disease from the reference group. (5) To justify the role of liver fat in brain ageing, we performed the analysis of the association of FLI and SLD with BAG, considering the effect of alcohol intake.

2.7.3 | Mediation Analysis

Generalised structural equation models (GSEM) were used to analyse the mediating role of INFLA in MASLD-BAG associations. Direct, indirect and total effects were estimated with confidence intervals through bias-corrected bootstrapping (50

TABLE 1 | Baseline characteristics of the study populations by metabolic dysfunction-associated steatotic liver disease (MASLD).

Characteristics	No MASLD/related SLD ($n=19351$)	MASLD/related SLD ($n=7360$)	MASLD/related SLD		
			MASLD ($n=5227$)	MetALD ($n=2104$)	Other ($n=29$)
Age at baseline (year)	54.58 ± 7.53	55.55 ± 7.26[a]	55.51 ± 7.34	55.65 ± 7.07	56.52 ± 6.70
Age at MRI assessment (year)	63.47 ± 7.68	64.30 ± 7.40[a]	64.21 ± 7.48	64.50 ± 7.20	65.76 ± 7.03
Female	11686 (60.39)	2059 (27.98)[a]	1597 (30.55)	456 (21.67)	6 (20.69)
Race-White	17975 (93.11)	6844 (93.20)	4825 (92.56)	1991 (94.76)	28 (96.55)
Townsend deprivation index	−2.68 (−3.91, −0.65)	−2.58 (−3.86, −0.47)[a]	−2.59 (−3.86, −0.48)	−2.57 (−3.85, −0.42)	−2.96 (−4.03, −0.47)
Education (college)	9583 (49.64)	3072 (41.86)[a]	2219 (42.56)	839 (40.05)	14 (48.28)
BMI (kg/m^2)	24.83 ± 2.86	30.55 ± 3.80[a]	30.69 ± 3.90	30.21 ± 3.51	30.41 ± 3.72
Waist circumference (cm)	82.67 ± 9.50	100.74 ± 8.60[a]	100.75 ± 8.69	100.68 ± 8.38	101.62 ± 7.68
Systolic BP (mm Hg)	132.97 ± 17.67	140.60 ± 16.30[a]	139.80 ± 16.25	142.66 ± 16.29	135.81 ± 11.91
Diastolic BP (mm Hg)	79.92 ± 9.66	85.71 ± 9.18[a]	85.21 ± 9.15	86.99 ± 9.12	84.72 ± 10.06
HbA1c	34.32 ± 4.22	36.19 ± 6.08[a]	36.32 ± 6.00	35.89 ± 6.32	35.29 ± 3.51
HDL-C (mmol/L)	1.59 ± 0.38	1.26 ± 0.28[a]	1.23 ± 0.26	1.33 ± 0.29	1.20 ± 0.22
Triglyceride (mmol/L)	1.34 ± 0.67	2.39 ± 1.14[a]	2.39 ± 1.13	2.37 ± 1.16	2.43 ± 1.06
Glucose-lowering drug use	292 (1.51)	520 (7.07)[a]	394 (7.54)	125 (5.94)	1 (3.45)
Lipid-lowering drug use	3147 (16.26)	2640 (35.87)[a]	1822 (34.86)	803 (38.17)	15 (51.72)
BP-lowering drug use	3656 (18.89)	2805 (38.11)[a]	1956 (37.42)	841 (39.97)	8 (27.59)
Alcohol drinking					
Never	522 (2.70)	180 (2.45)	178 (3.41)	0 (0.00)	2 (6.90)
Former drinker	400 (2.07)	195 (2.65)	194 (3.71)	0 (0.00)	1 (3.45)
Current drinker	18428 (95.24)	6984 (94.90)[a]	4854 (92.88)	2104 (100.00)	26 (89.66)
Smoking status					
Never	11989 (62.04)	4021 (54.80)[a]	3101 (59.45)	907 (43.33)	13 (44.83)
Former smoker	6198 (32.07)	2843 (38.74)	1829 (35.07)	1001 (47.83)	13 (44.83)
Current smoker	1137 (5.88)	474 (6.46)	286 (5.48)	185 (8.84)	3 (10.34)
Regular physical activity	14680 (78.04)	4822 (68.01)[a]	3385 (67.50)	1422 (69.50)	15 (51.72)
High level of social contact	7638 (39.57)	2853 (38.84)	1968 (37.70)	873 (41.63)	12 (41.38)
Cardiovascular disease	536 (2.77)	424 (5.76)[a]	310 (5.93)	113 (5.37)	1 (3.45)

(Continues)

TABLE 1 | (Continued)

Characteristics	No MASLD/related SLD ($n=19\,351$)	MASLD/related SLD ($n=7360$)	MASLD/related SLD		
			MASLD ($n=5227$)	MetALD ($n=2104$)	Other ($n=29$)
eGFR, mL/min/1.73 m^2	94.38 ± 12.09	89.71 ± 12.59[a]	89.06 ± 12.74	91.31 ± 12.05	89.54 ± 14.18
APOE ε4 carriers	4561 (27.56)	1702 (27.53)	1200 (27.40)	493 (27.71)	9 (39.13)

Note: Missing data: Education = 88; Race = 79; TDI = 26; Smoking = 59; Alcohol consumption = 10; Regular physical activity = 1002; Regular social contact = 79; BP = 946; HbA1c = 1524; HDL-c = 2672; eGFR = 21; *APOE* ε4 = 4566.
Abbreviations: *APOE* = *apolipoprotein* E, BMI = body mass index, BP = blood pressure, eGDR = glomerular filtration rate, HbA1c = haemoglobin A1c, HDL-C = high-density lipoprotein cholesterol.
[a]Significant difference between no MASLD/related SLD and MASLD/related SLD groups.

replications). Age, sex, education, race, TDI, BMI, smoking status, physical activity, social contact, cardiovascular disease, eGFR and *APOE* ε4 were controlled in the GSEM models.

3 | Results

3.1 | Baseline Characteristics of the Study Populations

The baseline characteristics of the 30 386 included participants (54.73 ± 7.48 years; 53.4% female) are summarised in Table 1. Among them, 5227 (17.0%) participants had MASLD, 2104 (6.9%) had MetALD and 29 (0.11%) had MASLD with other combined aetiology at enrollment. Compared to participants with no MASLD/related SLD, those with MASLD/related SLD were more likely to be older, male, non-college-educated, have lower SES, have cardiometabolic risk factors and cardiovascular disease, have lower eGFR, and be smokers, but less likely to have regular physical activity or to be drinkers.

3.2 | Association of MASLD and Its Subtypes With Brain Age Gap

The distribution of BAG in the total sample and in each MASLD group is shown in Figure S3. The mean (±SD) BAG was 0.39 ± 5.08 years and the median (P_{25}, P_{75}) was 0.22 (−2.93, 3.51) years. Brain age was on average 0.19 years older than chronological age for people without MASLD/associated SLD, and 1.07 years older for those with MASLD/associated SLD, particularly 1.87 years older than chronological age for those with MetALD. In the multi-variables adjusted model, MASLD/related SLD (β [95% CI] = 0.86 [0.70, 1.02]) was associated with significantly higher BAG, compared to no MASLD/related SLD (Table 2 and Figure S3). In particular, people with MASLD and MetALD had 0.59 (0.41, 0.77) and 1.57 (1.31, 1.83) years larger BAG than those without MASLD/related SLD. The results of basic-adjusted models were consistent (Table 2). In addition, NAFLD and MAFLD were both significantly associated with larger BAG, with β (95% CI) of 0.37 (0.19, 0.55) and 1.17 (1.02, 1.32), respectively (Table S9).

3.3 | Sensitivity Analysis

First, after stratifying by age (< 60 vs. ≥ 60 years), sex (female vs. male) and *APOE* ε4 status (carriers vs. non-carriers), the associations of MASLD/related SLD, MASLD and MetALD with significantly larger BAG remained (Figure 2 and Table S10). Notably, middle-aged adults with MetALD had nearly 2 years (β [95% CI] = 1.80 [1.49, 2.11]) older brain ageing than those without the condition. Second, after further adjustment for lipid-lowering medication use in multivariable-adjusted models, the MASLD-BAG association was consistent with the primary results (Table S11). Third, controlling for MRI head position and MRI assessment centre did not alter the MASLD-BAG associations (Table S12). Fourth, when we excluded participants with increased or excessive alcohol intake or with concomitant liver disease from the reference group, the association of MASLD/related SLD as well as its subtypes (MASLD and MetALD) with greater BAG remained significant (Table S13). Finally, the association of FLI and SLD with BAG was significant (Table S14). To address potential sex bias in FLI-based MASLD classification, we redefined MASLD using sex-specific FLI cut-offs (women: FLI ≥ 30; men: FLI ≥ 60). Sensitivity analyses revealed consistent associations between MASLD and accelerated brain ageing (Table S15), supporting the validity of our primary approach.

3.4 | The Mediating Role of Inflammation

The distribution of inflammation indices by MASLD/related SLD is shown in Figure S4; specifically, participants with MASLD/related SLD had higher INFLA. Also, the association between INFLA and BAG was significantly positive (Figure S5). The mediation analysis showed that INFLA partly mediated the association of MASLD/related SLD, MASLD and MetALD with BAG (Figure 3 and Table S16), and the mediation proportion was 13.53%, 20.14% and 7.13%, respectively.

Next, the study calculated the estimates of direct and indirect associations for specific subcomponents of INFLA (Table S17). Likely, WBC and CRP, among the inflammatory factors, are primary mediators in the association of MASLD/related SLD with BAG.

4 | Discussion

In this large-scale neuroimaging study with multimodal MRI phenotypes, we constructed a brain age prediction model based on LASSO regression and found that MASLD/related SLD, as well as its subtypes of MASLD and MetALD, were related to older brain age compared to chronological age. The

TABLE 2 | Standardised β coefficient and 95% confidence interval (CI) for the association of metabolic dysfunction-associated steatotic liver disease (MASLD) and its subtypes with brain age gap (BAG): Results from linear regressions.

MASLD	No. of participants	Mean ± SE	BAG			
			Basic-adjusted		Multi-adjusted	
			β (95% CI)	p	β (95% CI)	p
No MASLD/related SLD	19 351	0.19 ± 0.04	Reference	—	Reference	—
MASLD/related SLD	7360	1.07 ± 0.06	0.83 (0.69, 0.97)	< 0.001	0.86 (0.70, 1.02)	< 0.001
MASLD	5227	0.75 ± 0.07	0.54 (0.38, 0.70)	< 0.001	0.59 (0.41, 0.77)	< 0.001
MetALD	2104	1.87 ± 0.11	1.63 (1.41, 1.87)	< 0.001	1.57 (1.31, 1.83)	< 0.001
Other	29	−0.32 ± 0.91	−0.51 (−2.29, 1.28)	0.572	0.26 (−1.74, 2.25)	0.802

Note: Basic-adjusted models included age, sex and education. Multi-adjusted models additionally included race, socioeconomic status, smoking status, physical activity, social contact, cardiovascular disease, estimated glomerular filtration rate and *APOE* ε4.

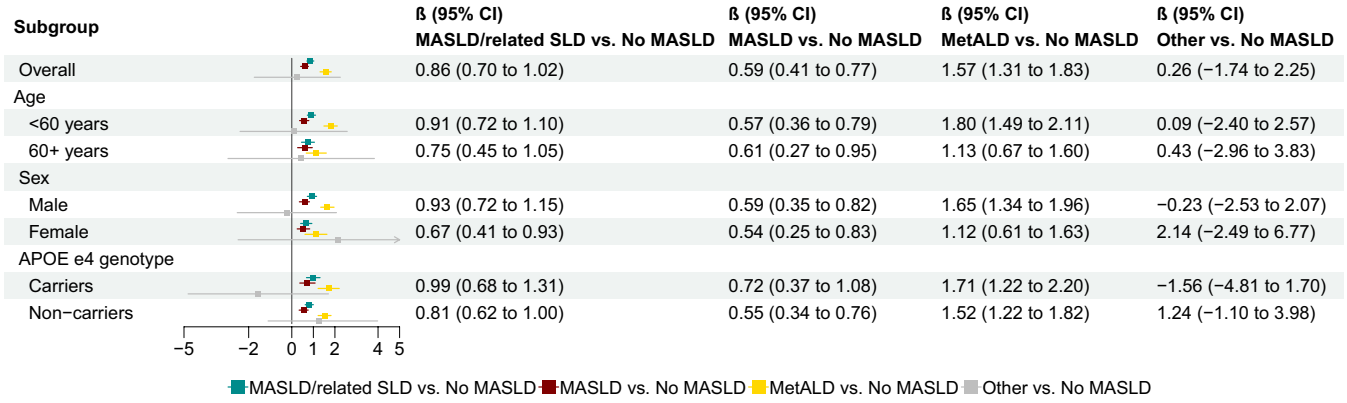

FIGURE 2 | Subgroup analysis for the associations of metabolic dysfunction-associated steatotic liver disease (MASLD) and its subtypes with brain age gap (BAG).

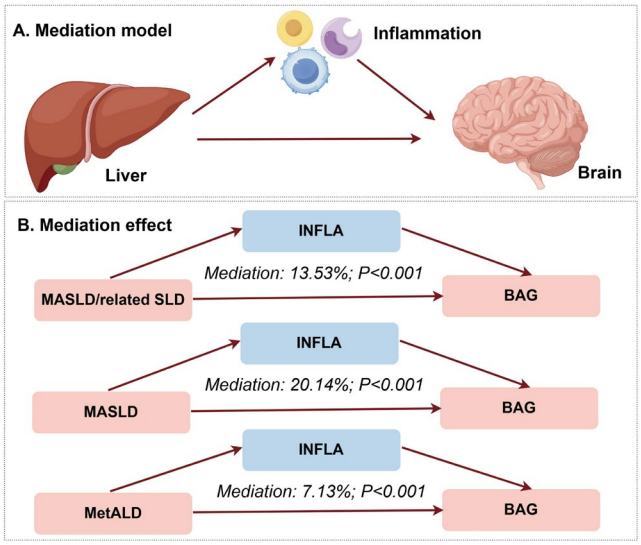

FIGURE 3 | Mediation effect of inflammation (INFLA) on the associations of metabolic dysfunction-associated steatotic liver disease (MASLD) and its subtypes with brain age gap (BAG). Models adjusted for age, sex, education, race, socioeconomic status, smoking status, physical activity, cardiovascular, estimated glomerular filtration rate and APOE ε4. Bootstrap was used to estimate the confidence intervals of mediation effects, and the number of iterations was 50.

MASLD-brain ageing associations were consistent regardless of age (< 60 and ≥ 60 years), sex (females and males) and *APOE* ε4 (carriers and non-carriers). In addition, participants with NAFLD and MAFLD also exhibited significantly accelerated brain ageing compared to those without any of these conditions. The deleterious associations between MASLD and brain ageing were partly mediated by low-grade systemic inflammation.

4.1 | Comparison With Previous Studies

Accumulative evidence suggests that NAFLD/MAFLD is associated with individual MRI measures, as manifestations of the 'liver-brain' axis. Several population-based imaging studies have found that NAFLD is associated with brain atrophy (total brain, grey matter and hippocampus) [8–10], cortical thickness reduction [11], cerebrovascular lesions [12–14] and cerebral blood flow reduction [37]. Some other animal experiments have shown that NAFLD/MAFLD is associated with cerebral hypoxia and total brain atrophy [38, 39]. However, inconsistent findings have also been obtained that NAFLD/MAFLD is not associated with cerebral lesions such as WMH, hippocampal atrophy, lacunas or brain infarcts [8, 9, 13]. No studies evaluated the association of MASLD with brain health, especially brain function and connectivity.

Previous studies have provided partial support for the link between liver disease and brain health, although they failed to adequately capture the extent of individual brain ageing. BAG based on multimodal MRI metrics integrates cerebral structural, functional and connectivity features, allowing for a more comprehensive picture of brain ageing [6]. In the present study, we found that MASLD/related SLD was associated with a 1.07 years older brain age than actual age and even nearly 2 years older when combined with increased alcohol intake. Since we used multimodal MRI data to estimate brain age, together with a large sample size, we were able to detect a highly statistically significant association between MASLD and higher BAG ($p < 0.001$). In light of conflicting results on the association between metabolic liver disorders and dementia [40, 41], our findings provide convincing evidence that MASLD may accelerate brain ageing even at the preclinical stage of neurodegenerative disease. MASLD affects more than a third of the world's adult population and is increasing dramatically [1]; therefore, MASLD management will create great differences in population health. MASLD could be largely avoided by managing metabolic risk factors via healthy lifestyles [1], and the potential benefits to brain health are likely to be additional gains from enhanced management in such populations.

Notably, our results showed that people with MetALD had a significantly larger BAG than other subtypes of MASLD/related SLD, which might be attributed to the detrimental impacts of excessive alcohol consumption on the brain. Heavy alcohol consumption has been associated with brain atrophy, loss of neurons and decline in white matter fibre integrity, and even moderate alcohol intake has an adverse association with global brain volume measures, regional grey matter volumes and white matter microstructure [42]. The cumulative effect of excessive drinking might be linked to its associated liver damage, which elevates serum iron and transferrin saturation and leads to a decrease in thiamine and increased iron permeability of the blood–brain barrier [43]. Moreover, dopamine surges and chronic inflammatory processes may also contribute to the potential mechanisms [43].

Considering the heterogeneity of the MASLD population, we further investigated the contribution of multiple other biological factors in the MASLD-brain ageing associations. After stratifying the study population according to age, sex, and *APOE* ε4 status, we found that the association between MASLD/related ALD and larger BAG was similar across subgroups (all *p for interaction* < 0.05). This finding may suggest the management and prevention of MASLD is crucial even for people with a lower genetic susceptibility to dementia and at younger ages, although this needs to be investigated in future studies.

4.2 | Potential Mechanisms

There are several biological mechanisms whereby MASLD may link to brain ageing. First, MASLD is also recognised as a chronic inflammatory disease [44]. As indicated by our mediation analyses, inflammation mediates the effects of MASLD on brain ageing. Low-grade systemic inflammation may lead to the activation of cerebral vascular endothelial cells and perivascular cells and change the permeability of the blood–brain barrier [45, 46], which in turn promotes a proinflammatory status and neuroinflammation in the central nervous system characterised by microglia and astrocyte activation. Persistent neuroinflammation disrupts synaptic plasticity, accelerates neuronal apoptosis and contributes to brain ageing [47]. Second, MASLD-associated hepatic mitochondrial impairment leads to excessive reactive oxygen species (ROS) production [48]. Systemic ROS overflow may compromise neuronal mitochondrial function, exacerbating oxidative damage to lipids, proteins and DNA in brain tissue. Third, insulin resistance is detected in approximately 40% of SLD patients, which is associated with dementia-related processes including clearance of the amyloid β peptide and phosphorylation of tau [49]. These multiple pathways reinforce each other and work together to contribute to neurodegeneration. Finally, metabolic risk factors are themselves independent risk factors for neurodegenerative diseases and brain ageing [50]. Future studies should employ advanced imaging techniques and plasma biomarkers to examine how MASLD severity affects brain ageing.

4.3 | Strengths and Limitations

Strengths of this study include the community-based design with a large sample size and a rigorous data collection procedure. Additionally, the availability of multimodal IDPs offers an opportunity to calculate brain age using machine learning models. Nonetheless, some limitations should be acknowledged. First, UK Biobank participants were volunteers, potentially representing a healthier subset of the general population [51]. Moreover, our analytical sample consisted of participants who underwent brain MRI scans and were free from chronic brain disorders, which is a relatively healthier subset in the overall UK Biobank population. This might have contributed to an underestimation of the magnitude of the association between MASLD and brain ageing. Furthermore, caution is required when generalising our results to populations outside of white European ancestry. Second, SLD is determined by FLI rather than liver biopsy or imaging. Although there is evidence that FLI is highly consistent with ultrasound diagnosis [18], misdiagnosis of MASLD may not be fully avoidable. Third, MASLD was only available at baseline; thus, we are unable to perform an analysis regarding the changes in MASLD and brain ageing. Finally, neuroimaging scans were not performed at baseline, so we cannot analyse the longitudinal association between MASLD and brain ageing trajectory.

5 | Conclusions

In conclusion, the present study provides evidence that MASLD/related SLD (including MASLD and MetALD) may contribute to accelerated brain ageing even in middle-aged adults and *APOE* ε4 non-carriers. Our study findings identified that about 13.53% of the MASLD-brain ageing association may be potentially prevented by addressing the low-grade systemic inflammation. Our findings highlight the need for managing MASLD in adults of any age, sex and genetic background, for promoting brain health.

Author Contributions

Drs Wang and Xu had full access to all the data in the study and take responsibility for the data analysis. Dr. Wang performed the literature

search and drafted the manuscript. Dr. Wang conducted the statistical analyses. All authors reviewed and edited the manuscript. All authors critically revised the manuscript for important intellectual content. All authors contributed significantly to finalising the manuscript and approved the final version for publication.

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Ethics Statement

The UK Biobank study received ethical approval from the National Health Service (NHS) National Research Ethics Service (Ref 21/NW/0157). All participants provided informed written consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analysed during the current study are available in the UK Biobank repository, http://www.ukbiobank.ac.uk.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.