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# Brain involvement in non-alcoholic fatty liver disease (NAFLD): A systematic review

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is associated with high cardiovascular morbidity and mortality which usually is considered to be related to cardiac involvement, while scarce attention is addressed to brain damage. Viceversa NAFLD is associated with asymptomatic brain lesions, alterations in cerebral perfusion and activity, cognitive impairment and brain aging and with increased risk and severity of both ischemic and haemorrhagic stroke. Besides known metabolic risk factors, NAFLD is characterized by a pro inflammatory state, which contributes to atherosclerosis and microglia activation, endothelial dysfunction, pro-coagulant state and platelets activation, which in turn promote both micro and macrovascular damage eventually responsible for clinical and subclinical cerebrovascular alterations. A better knowledge of the association between NAFLD and brain alterations could lead to an improved management of risk factors underpinning both liver and cerebral disease, possibly preventing the progression of asymptomatic brain lesions to clinical cerebrovascular accidents.



## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries and it will become the leading cause of liver transplant in next years. It is characterized by fat accumulation in more than 5% of hepatocytes in the absence of excessive alcohol intake or other causes of liver disease. It is a progressive disease, ranging from simple steatosis, to steatohepatitis (NASH), where inflammation may be associated to liver fibrosis and cirrhosis [1,2].

NAFLD patients are exposed to high morbidity and mortality, mostly consequent to cardiovascular (CV) accidents rather than liver-related complications [3,4]. In fact, NAFLD is associated with clinical and subclinical atherosclerosis [5–8], coronary artery disease [8,9], increased arterial wall stiffness [10,11], cardiac systolic and diastolic dysfunction and arythmia [12], as well as with increased epicardial adipose tissue (EAT) [13,14]. While the association of NAFLD with cardiac and vascular complications is widely reported in literature, less evidence is available on the association with stroke and even less with subclinical cerebrovascular disease [15,16].

The increased CV risk seems directly proportional to the severity of liver disease, especially in the presence of liver fibrosis, which has been demonstrated as the main prognostic determinant for long term outcome in NAFLD patients. In fact, a meta-analysis including 16 observational studies following up a total of 34,000 patients over a median of 6.9-years, confirmed that the presence of NAFLD (diagnosed by imaging or histology) confers an increased risk for fatal and non-fatal incident CV events and the greater the severity of NAFLD the higher the CV risk, even when adjusting for potentially confounding covariates [17].

The link between NAFLD and CV risk may be partly explained by the common metabolic features shared by both conditions, such as abdominal obesity, hypertension, atherogenic dyslipidaemia, insulin resistance and diabetes [18,19]. In addition, patients with NAFLD exhibit a range of non-traditional CV risk factors, including hyperuricaemia [20], hypoadiponectinaemia [21], as well as a pro-inflammatory and a pro-coagulant state which foster an unfavourable CV risk profile [22,23].

Also genetic background could promote CV risk even if the widely described patatin-like phospholipase domain-containing 3 (PNPLA3) polymorphism, believed to be the main genetic factor associated with NAFLD and associated with an increased risk of progressive liver disease and hepatocellular carcinoma, has not definitely been proved to influence CV risk [24–26]. On the contrary, another genetic polymorphism associated with a progressive liver disease, namely transmembrane 6 superfamily member 2

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(TM6SF2), has been widely demonstrated to confer a lower CV risk [27].

Therefore, we revised literature regarding the relationship between cerebrovascular involvement in patients with NAFLD, exploring a field where clear evidence is still missing. We searched full-text papers in PubMed database providing complete results on this issue. This topic is crucial considering the high prevalence of NAFLD and its potential adverse impact on cerebrovascular complications which may become a global severe health-system and economic burden worldwide.

## 2. Clinical cerebrovascular disease and NAFLD

Some interesting results on the association between NAFLD and cerebrovascular accidents are reported in literature, although data are often not conclusive. In addition, prevalence of NAFLD in patients experiencing cerebrovascular events is variable and its diagnosis is rarely based on histological data [5]. In the majority of cases hepatic steatosis is detected by imaging techniques (ultrasound-US or transient elastography), liver enzymes or fatty liver index (FLI), with a prevalence of 42–44% [28–31]; only one study reports a significantly lower prevalence of hepatic steatosis around 8% [32]. Prospective studies report a prevalence of NAFLD ranging from 18 to 36%, depending on different diagnostic tools used (i.e US or FLI) [33–35].

We depicted the most important evidences on the association between NAFLD and clinical cerebrovascular disease in Table 1.

In a study including 200 in-hospital patients with acute ischemic stroke, NAFLD was associated with the severity of cerebral accident at admission as assessed by the National Institutes of Health Stroke Scale (NIHSS), as well as with a worse functional outcome at discharge, as assessed by the Modified Ranking scale, a score commonly used to measure the degree of disability in the daily activities of people who have suffered a stroke [36]. However, in both cases, a multivariate analysis adjusted for known CV risk factors was not performed. Also Moshayedi et al. demonstrated that NAFLD, diagnosed by ultrasound, was more prevalent in ischemic stroke patients compared to a control group resulting a risk factor for cerebrovascular events in a sex and age adjusted analysis, but a multivariate analysis including other metabolic factors, smoking habits and the presence of chronic heart disease did not confirm this association. Nonetheless, the small simple size of this study [29] does not allow to draw sound conclusions. In a study from Greece examining 415 patients admitted to the hospital because of ischemic stroke, no association was found between NAFLD and neither an increased risk of stroke nor with its severity [32]. However, in this case prevalence of NAFLD was low and the diagnosis of NAFLD was based on altered liver function tests which are neither sensitive nor specific for the diagnosis of NAFLD [37]. Finally, in a prospective population-based cohort study of 30,239 black and white adults of 48 years mean age [35], designed to investigate racial and regional disparities in cerebrovascular accidents in the United States, NAFLD (diagnosed by fatty liver index (FLI) >60 and increased transaminases) was inversely associated with stroke risk in men, while higher gGT and FLI values were positively associated with stroke risk in women. In addition, an AST/ALT ratio >2 demonstrated a positive association with stroke in whites but not blacks [30]. These uneven results may be again due to the scarce sensitivity of the tests used for the diagnosis of NAFLD, as well as to racial and hormonal gender-related differences. Another study including 6340 subjects without pre-existing CV disease addressing the risk of CV endpoints including stroke, suggested an inverse association of NAFLD diagnosed by FLI, in subjects older than 50 years, and a positive association in younger people.

In contrast with these data, some other evidence more clearly supports the association between NAFLD and increased stroke risk. In a Chinese study including patients with acute brainstem infarction (BSI), initial NIHSS, incidence of progression and stroke severity were significantly higher in patients with NAFLD than in those without NAFLD, even when adjusted for confounding factors [38]. In a retrospective study comparing 295 patients with ischemic stroke and 1942 healthy controls, both with a high prevalence of steatosis, liver fibrosis defined by liver stiffness measurement (LSM) resulted a risk factor for stroke independently of age, steatosis grade and other CV risk factors even when the propensity score matched analysis [31] was performed.

Moreover, three prospective observational studies explored the relationship between NAFLD and cardiovascular disease, including both cardiac and cerebral districts, and found a significant correlation with cardiovascular accidents suggesting a harmful effect of NAFLD in this setting [5,33,34]. In the study by Hamaguchi et al., including 1221 apparently healthy Japanese men and women recruited from a health check-up program, and followed-up for 24-months the occurrence of both cardiac and cerebrovascular accidents was higher in subjects with than in those without NAFLD, and NAFLD remained a predictor of cardiovascular disease independently of conventional risk factors [34]. However, the outcome was assessed by a self-administered questionnaire and the main difference in the incidence of cardiovascular accidents was observed for cardiac events rather than cerebrovascular ones. In another study with more than 700 patients without previous CV events followed-up over a 3-year period, 36% of the cohort experienced a CV event, 53% of whom a cerebrovascular accident [33], and NAFLD remained an independent risk factor for CV events. Finally, in the study by Fracanzani et al. a total of 91 biopsy-proven NAFLD patients and a matched control group of 182 healthy subjects, were followed-up for 10 years and the presence of NAFLD was an independent risk factors for CV events, both cardiac and cerebrovascular [5].

In the metanalysis by Hu et al., which included 7 independent studies (including also the abovementioned prospective studies) with a total of 6183 subjects, a significant association of NAFLD with elevated risk of cerebrovascular accidents was reported, and the risk was confirmed also when the analysis was stratified by ethnicity, accident classification and study design. However, either the prevalence of NAFLD or methods by which steatosis was diagnosed are not reported and differences in adjusted factors in the multivariate analysis of the various studies did not allow to reach a definite conclusion [39]. Hadda et al. included prospective studies with a total of 25,800 subjects, and confirmed an increased number of CV events in NAFLD compared to the control group with a significant difference in the number of cerebrovascular events [40]. Also in this case, the heterogeneity of the studies, variability in outcome definition and follow-up may have hampered the impact of the final results.

In conclusion, despite NAFLD seems associated with an increased risk and severity of both clinical or asymptomatic (brainstem infarction) stroke, as well as with a worse functional outcome, further prospective studies considering as unique endpoint ischemic/haemorragic stroke are needed to confirm these results.

## 3. Subclinical cerebrovascular disease and NAFLD

If data on overt cerebrovascular damage are scarce and not conclusive, results on subclinical cerebrovascular alterations are even less established. In addition, prevalence of NAFLD in patients with subclinical brain disease is difficult to be determined since the majority of studies are case-control. In few cross-sectional studies available, presence of NAFLD detected by with imaging techniques is approximately 18% [41,42].

All studies reporting the association between NAFLD and subclinical cerebrovascular disease are listed in Table 1.

**Table 1**
Studies addressing the association between NAFLD and cerebrovascular disease.

| Study considering: | Year | Country | Ethnicity | Sample size | Study design | NAFLD diagnosis | Prevalence of NAFLD | Parameters evaluated | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Cognitive alterations | | | | | | | | | |
| Seo et al. [41] | 2016 | Korea | Asiatic | 4472 subjects from the NHANES III study | Cross sectional | US, liver enzymes | 19% | Cognitive performance by computerized tests (SRTT, SDST and SDLT) | NAFLD is associated with lower SDLT (beta coefficient 0.726, CI 95% 0.105-1.347) |
| Tuttolomondo et al. [48] | 2018 | Italy | Caucasian | 80 NAFLD patients<br>83 subjects without liver or CV disease | Case control | Liver biopsy | – | Cognitive performance by paper test (MMSE) | NAFLD is associated with lower MMSE (OR 24.9, $p < 0.001$). No difference according to presence of NASH or severity of fibrosis |
| Brain alterations | | | | | | -Vascular | | | |
| Takahashi et al. [44] | 2017 | Japan | Asiatic | 24 NAFLD patients<br>15 healthy subjects | Case control | US, liver enzymes | – | Cerebral perfusion by oxy-Hb by NIRS | Lower cerebral perfusion in patients with NAFLD vs controls ($P < 0.001$). No multivariate analysis performed |
| Airaghi et al. [15] | 2018 | Italy | Caucasian | 17 NAFLD patients<br>17 healthy subjects | Case control | Liver Biopsy | – | Cerebral perfusion by MRI spectroscopy | NAFLD is associated with low cerebral perfusion (beta coefficient 5.7; 95% CI −11, −0.08, p 0.046) |
| Tuttolomondo et al. [48] | 2018 | Italy | Caucasian | 80 NAFLD patients<br>83 subjects without liver or CV disease | Case control | Liver biopsy | – | Arterial stiffness by PWV and AIH<br>Endothelial dysfunction by RHI | NAFLD is associated with lower AIH (OR 4.7, $p = 0.032$). No difference according to presence of NASH or severity of fibrosis |
| -Subclinical tissue lesions | | | | | | | | | |
| Petta et al. [47] | 2016 | Italy | Caucasian | 79 NAFLD patients<br>82 subjects without liver or CV disease | Case control | Liver biopsy | – | Cerebral white matter lesions (WML) by MRI | NAFLD is not associated with WML, differently from fibrosis $\geq$ F2 (OR 3.36, CI 95% 1.29–8.73; $p = 0.01$) |
| Weinstein et al. [42] | 2018 | Israel | Caucasian | 766 subjects from the Framingham study | Cross sectional | CT scan | 17.9% | Cerebral brain volume, hippocampal and white matter hyperintensity, covert brain infarctions by MRI | NAFLD is associated with lower total brain volume (beta coefficient −0.26 (0.11), $p = 0.02$) |
| Clinical events | | | | | | | | | |
| Moshayedi et al. [29] | 2014 | Iran | Caucasic | 110 patients with clinical presentation of ischemic stroke<br>110 healthy subjects | Case control | US | 42.7% (in patients)<br>23% (in controls) | Imaging (CT or MRI) confirmed Ischemic stroke | NAFLD is risk factor for stroke in a sex and age adjusted analysis (OR 2.15; CI 95% 1.25–3.71; p00.006), but not in multivariate analysis (OR 1.68; CI 95% 0.42–6.75; $p = 0.46$) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Alexander et al. [30] | 2017 | USA | Caucasian | Participants from REGARDS study): 572 with clinical presentation of ischemic stroke 1104 stroke free cohort random sample (CRS) | Case cohort | Fatty liver index (FLI) Liver enzymes | 44% (in CRS) | Clinical presentation ischemic stroke | NAFLD is associated with reduced risk of stroke in men (OR 0.5, CI 95% 0.26–0.96). When considered FLI as continuous variables, women in the top 10% of FLI score are at increased risk of stroke (OR 2.26, CI 95% 1.14–4.47) |
| Kim et al. [31] | 2017 | South Korea | Asiatic | 295 patients with clinical presentation of ischemic stroke or TIA 1942 healthy subjects | Case control | Transient elastography | 42.4% (patients) 41% (controls) | Imaging (CT or MRI) confirmed Ischemic stroke | Liver fibrosis expressed as liver stiffness measurement (LSM) is associated with increased risk of stroke (for every 1 kPa increase: OR 1.29, CI 95% 1.18–1.36; $p < 0.001$). |
| Disability and outcome of clinical events | | | | | | | | | |
| Tziomalos et al. [32] | 2013 | Greece | Caucasian | 415 patients with ischemic stroke | Cross sectional | Liver enzymes (confirmed by US) | 7.7% | Disability by NIHSS at admission and mRS at discharge Length of hospitalization In-hospital mortality | NAFLD is not associated with worse NIHSS ($p = NA$), mRS ($p = NA$); not associated with higher length of hospitalization ($p = NA$) and in-hospital mortality ($p = NA$). |
| Abdeldyem et al. [28] | 2017 | Egypt | African | 200 patients with ischemic stroke | Cross sectional | Liver enzymes (confirmed by US) | 42.5% | Disability by NIHSS at admission and mRS at discharge | NAFLD is associated with higher NIHSS at admission ($p = 0.013$) and higher mRS at discharge ($p = 0.009$). No multivariate analysis performed |
| Li et al. [38] | 2018 | China | Asiatic | 306 patients with brainstems infarctions (BSIs) | Cross sectional | Liver enzymes (confirmed by US) | 42.5% | Stroke severity (NIHSS > 7 at admission) Stroke progression (NIHSS $\geq$ 1 or 2 points between admission and discharge) Adverse outcome (mRS $\geq$ 3 at discharge) | NAFLD is associated with stroke severity of BSIs (HR 2.32; CI 95% 1.25-4.32; $p < 0.001$) and its progression (HR 2.38, CI 95% 1.26–4.49, $p < 0.001$) |

Table 1 (*Continued*)

| Study considering: | Year | Country | Ethnicity | Sample size | Study design | NAFLD diagnosis | Prevalence of NAFLD | Parameters evaluated | Findings |
|---|---|---|---|---|---|---|---|---|---|
| Both cardiac and cerebral events | | | | | | | | | |
| Hamaguchi et al. [34] | 2007 | Japan | Asiatic | 1637 healthy subjects | Prospective | US | 18.9% | Coronary artery disease; ischemic stroke<br>Cerebral haemorrhage | NAFLD is associated with increased risk of incident CV events (OR 7.32 ; 95% CI 1.22–43.8; p = 0.003) |
| El Azeem et al. [33] | 2013 | Egypt | African | 747 subjects without previous CV events | Prospective cohort study | US | 35.8% | Coronary artery disease<br>Ischemic stroke<br>Cerebral haemorrhage | NAFLD is associated with increased risk of incident CV events (OR 5.21; CI 95% 1.93–4.25 p < 0.001) |
| Fracanzani et al. [5] | 2016 | Italy | Caucasic | 91 NAFLD<br>182 healthy subjects | Prospective | US<br>Liver biopsy | | Carotid damage<br>CV events (including stroke and TIA) | Mean progression rate of cIMT is higher in controls than NAFLD, as well as incidence of carotid plaques (p = 0.002).<br>NAFLD is associated with increased risk of CV events (HR 1.99; CI 95% 1.01-3.94; p = 0.04) |
| Kunutsor et al. [35] | 2017 | Netherlands | Caucasic | 6340 subjects from the PREVEND cohort without previous CV events | Prospective | FLI<br>HIS (hepatic steatosis index) | 24% (by FLI)<br>31 % (by HSI) | CV events (including stroke) | NAFLD is associated with an increased risk of incident CV events in the in age < 50 ys (HR 1.63; 95% CI: 1.08 to 2.65; P = 0.024) and with a reduced risk in age>50 ys (0.75; CI 95% 0.56-0.9; p < 0.001). |
| Hu et al. [39] | 2017 | China | 6 studies Caucasian<br>3 studies Asiatic | 6183 total subjects (7 studies) | Meta-analysis (2 case-control and 7 cohort studies). | NA | NA | CV events (including ischemic stroke and cerebral haemorrhage) | NAFLD is associated with increased risk of cerebral haemorrhage (OR 1.85, 95% CI 1.05–3.27; p = 0.034) and ischemic stroke (OR 2.51, 95% CI 1.92–3.28; p < 0.001). Results confirmed also when analysis is stratified by ethnicity, accident classification and study design |
| Haddad et al. [40] | 2017 | USA | Caucasian | 25,837 total subjects (6 studies) | Meta-analysis (all prospective studies) | NA | 23% | CV events (including ischemic stroke and cerebral haemorrhage in only 3 studies) | NAFLD is associate with increased risk of clinical CV events (OR 1.77, 95% CI 1.26–2.48; p < 0.001);<br>NAFLD is associate with increased risk of stroke (RR 2.09, 95% CI 1.46–2.98; p < 0.001) |

Abbreviations: NAFLD: non-alcoholic fatty liver disease; MRI: magnetic resonance imaging; US: ultrasound; CT: computer tomography; NIRS: near infrared spectroscopy; WML: white matter lesions; SRTT: simple reaction time test; SDST: symbo-digit substitution; SDLT: serial digit learning test; MMSE: mini mental state examination; PSW: pulse wave velocity; AIH augmentation index; RHI: reactive hyperemia index; NASH: non-alcoholic steatohepatitis; NIHSS: National Insitute of Health Stroke Scale; mRS: modified Ranking Scale; FLI: fatty liver index; HIS: hepatic steatosis index; CV: cardiovascular; TIS: transient ischemic attack; cIMT: carotid intima-media thickness; OR: odd ratio; CI: confidential interval HR: hazard ration; RR: relative ratio; NA: not available

In a small Italian group of patients affected by NAFLD, hepatic steatosis has been demonstrated associated with reduced cerebral perfusion confined to limited brain areas, i.e left semioval centre and posterior cingular cortex, diagnosed by spectroscopy MRI and perfusion techniques. This association remained significant independently of features of metabolic syndrome (lipid profile, hypertension, BMI) and histological severity [15]. Interestingly, these cerebral areas with decreased blood perfusion are supplied by the left middle cerebral area, which is the most frequent vessel involved in ischemic stroke, thus suggesting a subclinical cerebral damage in areas more susceptible to ischemic damage. A decreased cerebral perfusion has been reported also in patients affected by chronic hepatitis C, possibly due to ischemic damage HCV related [43].

Another small study from Japan demonstrated in 24 NAFLD female patients a reduced brain activity, directly related to cerebral blood volume, which was measured as oxygenated haemoglobin (oxy-Hb) concentration in the blood by near-infrared spectroscopy (NIRS). In this study, the NIRS showed a decrease in cerebral oxy-Hb concentration in the frontal lobe and the number of words spoken in response to a verbal function test was lower in NAFLD patients compared to healthy controls [44]. In addition, a questionnaire to assess the depressive state administered to both NAFLD patients and controls before the NIRS assessment was not different between the groups, thus suggesting that a decrease in brain activity in NAFLD may occur before the patients experience depression. In addition, the decline in cognition function may explain the decrease in number of words and oxy-Hb concentration during the verbal function test in NAFLD patients.

Another study which used MRI demonstrated that NAFLD is linked to morphological cerebral alterations, possibly attributed by Authors to brain aging [42]. This study evaluated the association between NAFLD and brain imaging measures, particularly regarding total cerebral brain volume, white matter hyperintensity volume and presence of covert brain infractions, which correlate with cognitive performance and predict future risk of dementia, stroke and mortality [45] and found that patients with NAFLD had a significantly lower cerebral brain volume [42] after adjustment for confounding factors. Furthermore, when the estimated years of brain aging associated with NAFLD was evaluated in patients younger than 60 years, the difference in brain volume between people with and without liver steatosis corresponded to 7 years of brain aging, and to 4 years in the older patients. However, besides aging, cerebral atrophy could be consequent also to metabolic and microvascular alterations linked to NAFLD. Other evidence show that in NAFLD patients cerebral white matter lesions, considered manifestations of cerebral small vessels disease and linked to increased risk of stroke, cognitive decline and mortality [46], are proportioned to the severity of liver disease. Petta et al. demonstrated the presence of cerebral white matter lesions, mainly localized in the frontal cortex, in a NAFLD cohort of 79 patients and that prevalence of cerebral lesions was higher in patients with more severe liver disease (NASH and advanced fibrosis). Moreover, the presence of fibrosis, but not that of simple steatosis or NASH, was associated with a two-fold increase in the risk of cerebral lesions when adjusted for known CV risk factors and for increased carotid intima-media thickness values (cIMT). Probably, the proinflammatory and proatherogenic state characteristic of advanced liver disease may explain the higher risk of developing cerebrovascular alterations in patients with more severe liver disease [47].

Besides early stage of cerebral alterations, NAFLD has also been associated with worse performance in the cognitive assessment evaluated by mini-mental status test (MMSE) [48], which indeed is not a real neuropsychological test but it is widely used as surrogate of cognitive performance, along with endothelial alterations evaluated by reactive hyperemia index (RHI) and arterial stiffness. The study by Tuttolomondo et al. speculated that lower MMSE values found in subjects with NAFLD may be indicative of a lower degree of cognitive performance even in the absence of MMSE scores indicating a clinical cognitive dysfunction, i.e <24 (mean MMSE $26.9 \pm 1.6$ in NAFLD vs $28 \pm 1.4$ in controls). In addition, to lower MMSE values, patients with NAFLD had higher degree of arterial stiffness and reduced endothelial mediated vasodilation, thus highlighting an early stage of vascular damage related to subclinical cognitive impairment. Another group from Korea, confirmed the association between NAFLD and cognitive impairment in a wide epidemiological study [41]. They analysed a group of 4472 patients aged 20–59 yrs from the Third National Health and Nutrition Examination Survey (NHANES III), 874 of whom were diagnosed to have NAFLD by ultrasound. All subjects were submitted to three computer-administered tests to evaluate their cognitive function with particular regard to psychomotor speed, visual attention, learning, recall and concentration function. Patients with NAFLD presented lower performance in the cognitive tests related to learning, recall and concentration function, independently of metabolic and cardiovascular risk factors, age and education compared to those without NAFLD. Therefore, the Authors speculated that NAFLD might affect brain function through region-specific processes rather than diffuse cortical dysfunction.

Despite very promising and interesting results which highlight the association of NAFLD with subclinical cognitive impairment and brain lesions, all the reported studies do not present a prospective design, thus not allowing the determination of a temporal sequence between NAFLD onset and brain MRI alterations. In addition, the different diagnostic criteria for NAFLD used in the various studies may have included selection bias in the population studied.

## 4. Link between NAFLD and cerebrovascular disease: possible mechanisms

NAFLD is characterized by high cardiovascular mortality [17] by promoting an unfavourable risk profile through several mechanisms.

Liver and cerebrovascular diseases share common metabolic risk factors, namely insulin resistance, hypertension, obesity, physical inactivity and dislipidemia [49]. All these risk factors associated with NAFLD have been reported to accelerate cerebral small vessel disease, resulting in white matter lesions, cerebral microhaemorrhage, and brain atrophy [50,51].

In addition, NAFLD is characterized by different degrees of inflammation which increases platelet activity, pro-coagulant imbalance and endothelial dysfunction, leading to cerebral vessels and microvascular alterations (Fig. 1) [49,52,53]. Inflammation increases cytokines and up-regulates pro-atherogenic transcription factors [54,55], promoting systemic subclinical vascular disease [56] and vessels atherogenic lesions [57]. Along with these effects, the inflammatory state might affect the homeostasis of small cerebral vessels and increase number of activated microglia cells in the brain, thus creating microvascular structural alterations and neurotransmitters impairment and possibly favouring cerebral peripheral ischemia and neurodegeneration, as shown in animal models [58,59]. Clinical data also support the association between inflammation and both endothelial dysfunction and microvascular disease. In a recent study involving more than 2200 participants, the association of NAFLD with microvascular dysfunction, identified as low brachial artery flow-mediated dilation and low fingertip peripheral arterial tonometry, was significant even after adjustment for vascular risk factors and visceral adiposity [60]. Such microvascular alterations may be applicable also to the brain circulation, possibly impairing the cerebral blood flow and supply,

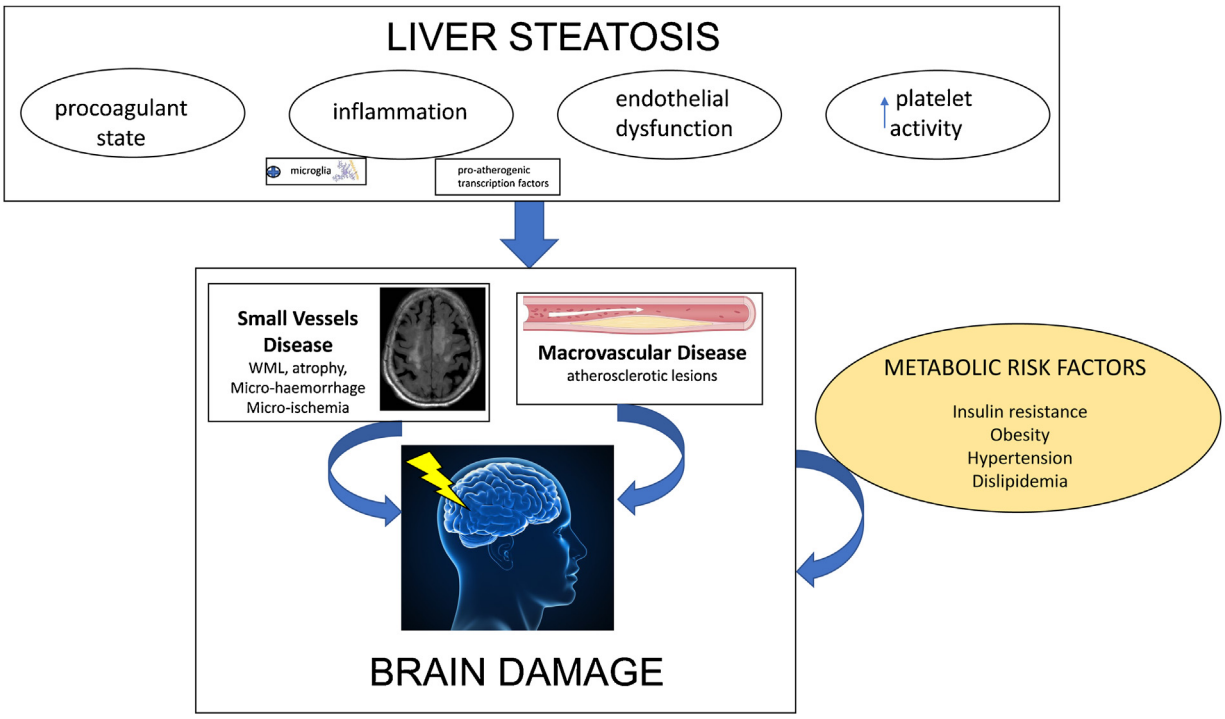


**Fig. 1.** The possible mechanisms underlying the association between NAFLD and cerebrovascular damage are depicted. Liver steatosis is characterized by a pro inflammatory state, which fosters atherosclerosis and microglia activation, along with endothelial dysfunction, pro-coagulant state and platelets activation. These effects promote both micro and macrovascular damage, which in turns are responsible for clinical and subclinical cerebrovascular alterations. In addition, also classic metabolic risk factors may concur to this unfavourable cerebrovascular profile.

subsequently leading to microvascular ischemia, brain tissue damage, atrophy and cognitive impairment.

In addition, also increased arterial stiffness may play a role in the onset of cerebral accidents and degeneration. A meta-analysis performed a few years ago, including 10 studies with a total of 22,400 patients, showed that the higher the carotid stiffness, evaluated by ultrasound, the higher the risk for stroke independently of aortic stiffness and mean arterial pressure [11]. Since NAFLD patients present increased carotid stiffness [61], we can speculate that this vascular alteration may contribute to stroke predisposition. In particular, stiffening of carotid walls leads to higher pulsatile pressure and flow load to the brain which eventually will damage microcirculation causing cerebral ischemia and haemorrhage, as well as hypertrophic remodelling response of small cerebral arteries responsible for chronic ischemia. In a study enrolling 1800 subjects, carotid stiffness was independently associated with brain lacunar infarctions and white matter hyperintensity (diagnosed by MRI), which are believed to result from cerebral ischemic small vessels disease [62]. Furthermore, data in literature showed an association between carotid stiffness and presence and composition of carotid atherosclerotic plaques, in particular intraplaque haemorrhage, especially in the internal carotid artery [63]. Finally, arterial stiffness has also been reported associated with cognitive impairment in elderly people [64].

## 5. Conclusions

Data in literature suggest a role for NAFLD in promoting both early cerebral alterations with cognitive impairment, subclinical ischemic lesions and cerebrovascular accidents. However, results concerning prevalence of NAFLD in patients with stroke or asymptomatic brain lesions and association between liver disease and severity of cerebral alterations are multifaceted and often contrasting, thus preventing conclusive assumptions.

In fact, despite NAFLD seems associated with an increased risk and severity of stroke, both clinical or asymptomatic (brainstem infarction), as well as with a worse functional outcome, prospective studies with ischemic stroke or cerebral haemorrhage as unique endpoints are still missing. In addition, although very promising and interesting results highlight the association of NAFLD with subclinical cognitive impairment and subclinical brain lesions, all the reported studies present a cross-sectional or case-control design, making impossible the determination of a temporal sequence between NAFLD and brain alterations.

Prospective studies including wide cohorts of patients are warranted to confirm and increase the knowledge on the association between NAFLD and brain alterations. This would promote a better management of risk factors underpinning both liver and cerebral disease, possibly preventing the progression of asymptomatic brain lesions to clinical cerebrovascular accidents in patients with NAFLD.

## Conflict of interest

None declared.

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