Letter to the Editor

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Changing from NAFLD through MAFLD to MASLD: Similar prevalence and risk factors in a large Brazilian cohort

To the Editor:

We read with great interest the multi-society statement on new fatty liver disease nomenclature published by the NAFLD Nomenclature Consensus Group.[1] The term non-alcoholic fatty liver disease (NAFLD), formerly metabolic dysfunction-associated fatty liver disease (MAFLD),[2] will now be metabolic dysfunction-associated steatotic liver disease (MASLD). Additionally, metabolic dysfunction-associated steatohepatitis (MASH) will replace the term non-alcoholic steatohepatitis (NASH). We aimed to compare the burden of the fatty liver disease in participants from the ELSA-Brasil study using the different nomenclature/criteria.

Briefly, the ELSA-Brasil study is an ongoing multicentric cohort that included 15,105 public servants from six cities in Brazil (aged 35-74 years-old; 46% male; 30% with BMI >30 kg/m^2) from 2008 to 2010. All participants were assessed by clinical evaluation, blood tests and abdominal ultrasound.[3] Fatty liver, now named steatotic liver disease (SLD), was diagnosed by high-resolution ultrasound B-mode images that were recorded and centrally read. NAFLD was defined by the presence of SLD in the absence of excessive alcohol consumption (<140 g/week for women and <210 g/week for men) or other chronic liver diseases.[4] MAFLD was defined as the presence of SLD with overweight/obesity (BMI ≥25 kg/m^2), type 2 diabetes or presence of metabolic dysregulation.[2] MASLD was defined as SLD with at least one cardiometabolic risk factor without excessive alcohol intake. Additionally, other subcategories of SLD, such as MetALD and cryptogenic/other SLD, were defined in the new statement.[1] The Kappa index (standard error) was used for the concordance analysis between different classifications of fatty liver disease. Participants were excluded due to recorded images of inadequate quality for centralized reading (n = 1,830), missing ultrasound imaging (n = 2,608) or missing data (n = 16) (Fig. S1).

Therefore, 10,651 individuals (44% male; median age 51 [IQR 45–58] years, median BMI 26.5 [23.9–29.6] kg/m^2 and median alanine aminotransferase 23 [18-32] IU/L; 15% with diabetes and 31% with metabolic syndrome) were included in this analysis. Overall, the prevalence of NAFLD, MAFLD and MASLD was 34.7% (95% CI 33.8-35.6, n = 3,697), 34.9% (95% CI 34.0–35.8, n = 3,718) and 33.4% (95% CI 32.6-34.4, n=3,569), respectively. People with fatty liver disease were significantly older, more frequently male and had significantly higher levels of glucose, lipid profile, HOMA-IR and liver enzymes compared to those without fatty liver disease regardless of whether they were classified as having NAFLD, MAFLD or MASLD (Table 1). Of those with NAFLD, 3.5% (n = 128/3,697) were not classified as having MASLD. All these individuals would be classified as having cryptogenic-SLD by the new nomenclature. On the other hand, all participants without NAFLD (no-NAFLD) were also classified as not having MASLD (no-MASLD). Additionally, 7.9% (n = 293/3,697) of those with NAFLD would not be classified as having MAFLD and 4.5% (n = 314/6,954) without NAFLD would be categorized as having MAFLD. From those with MAFLD (n = 3,718), a total of 320 participants (8.6%) were not classified as having MASLD. Of them, 98.1% (n=314) would be classified as having MetALD and 1.9% (n = 6) as having cryptogenic-SLD. All six participants with MAFLD but cryptogenic SLD had insulin resistance (HOMA-IR ≥2.5) and high levels of high-sensitivity C-reactive protein (>2 mg/dl) without overt cardiometabolic risk factors. Otherwise, 2.5% (n = 171/6,933) of people without MAFLD would be classified as having MASLD. The Kappa values (standard error) for the concordance analyses were 0.973 (0.010) between NAFLD and MASLD classifications; 0.900 (0.010) between MAFLD and MASLD and 0.874 (0.010) between NAFLD and MAFLD (Table S1).

We showed a high burden of SLD in a multicenter study from Brazil. More importantly, our findings showed that, at least in this sample, there was not a significant difference in the prevalence and factors associated with SLD, whether using NAFLD, MAFLD or MASLD criteria. Our findings reinforced that this change in the nomenclature will benefit the field without impacting the validity of the evidence published using the NAFLD term in the last decades. We acknowledge that the term MAFLD would be an affirmative term to describe the liver disease associated with known metabolic dysfunction rather than NAFLD.[2] However, the potential impact of the excessive use of alcohol in this liver disease was not considered in these criteria. We agree with the consensus group that MASLD would be an affirmative and non-stigmatizing name that improves upon the terms NAFLD or MAFLD. A recent study suggested that MASLD would be associated with higher mortality rates and incident cardiovascular disease.[5] However, further longitudinal studies will be needed to assess the incidence of liver- and non-liver-related complications and the prognostic value of advanced fibrosis in each sub-type of this new classification. Beyond this fact, regulatory approval of therapies for steatohepatitis-related fibrosis has been hindered by several challenges including population heterogeneity and lack of validated non-invasive biomarkers to assess fibrosis response after treatment. Despite the similar prevalence of liver disease regardless of the criteria used, this new nomenclature defined by a multi-society Delphi process and proposed by a panel of experts will help to better differentiate people with pure MASLD from those with metabolic liver disease associated with alcohol intake (MetALD). Use of the term MASLD instead of NAFLD will support regulatory claims for drug development and the

Table 1. Characteristics of participants included in the analysis according to the criteria used to define the fatty liver disease.

	All (N = 10,651)	No-NAFLD (n = 6,954)	NAFLD (n = 3,697)	*p* value	No-MAFLD (n = 6,933)	MAFLD (n = 3,718)	*p* value	No-MASLD (n = 7,082)	MASLD (n = 3,569)	*p* value
Male sex at birth[a]	4,687 (44.0)	2,889 (41.5)	1,798 (48.6)	<0.001	2,751 (39.7)	1,936 (52.1)	<0.001	2,940 (41.5)	1,747 (48.9)	<0.001
Age, yr[b]	51 (45-58)	50 (45-58)	52 (46-59)	<0.001	50 (44-58)	53 (46-59)	<0.001	50 (44-58)	52 (46-59)	<0.001
Excessive alcohol intake[a]	726 (6.8)	726 (10.4)	0 (0.0)	<0.001	412 (5.9)	314 (8.4)	<0.001	726 (10.3)	0 (0.0)	<0.001
Metabolic features										
BMI, kg/m^2[b]	26.5 (23.9-29.6)	25.5 (23.1-28.2)	28.7 (25.9-31.9)	<0.001	25.1 (22.9-27.8)	29.1 (26.6-32.3)	<0.001	25.4 (23.1-28.1)	28.9 (26.2-32.2)	<0.001
WC, cm[b]	89.9 (81.7-98.5)	87 (79-95)	96 (89-104)	<0.001	86 (79-93)	98 (91-105)	<0.001	86 (79-94)	97 (90-105)	<0.001
Systolic BP, mmHg[b]	119 (109-130)	116 (107-128)	122 (113-133)	<0.001	116 (107-127)	123 (114-135)	<0.001	117 (107-128)	123 (113-134)	<0.001
Diastolic BP, mmHg[b]	75 (69-83)	74 (67-81)	78 (71-85)	<0.001	73 (67-80)	79 (72-86)	<0.001	74 (67-81)	78 (72-85)	<0.001
Type 2 diabetes[a]	1,631 (15.3)	756 (10.9)	875 (23.7)	<0.001	667 (9.6)	964 (25.9)	<0.001	757 (10.6)	874 (24.8)	<0.001
Hypertension[a]	4,620 (43.4)	2,603 (37.4)	2,017 (54.6)	<0.001	2,416 (34.8)	2,204 (59.3)	<0.001	2,603 (36.8)	2,017 (56.5)	<0.001
Metabolic syndrome[a]	3,266 (30.8)	1,482 (21.4)	1,784 (48.3)	<0.001	1,303 (18.9)	1,963 (52.9)	<0.001	1,482 (21.0)	1,784 (50.1)	<0.001
Biochemistry										
Fasting glucose, mg/dl[b]	100 (93-108)	98 (92-106)	103 (96-112)	<0.001	98 (92-105)	104 (97-114)	<0.001	98 (92-106)	103 (97-113)	<0.001
HbA1c, %[b]	5.2 (4.9-5.6)	5.2 (4.9-5.6)	5.4 (5- 5.8)	<0.001	5.2 (4.9- 5.5)	5.4 (5- 5.8)	<0.001	5.2 (4.9- 5.5)	5.4 (5.0- 5.8)	<0.001
Total cholesterol, mg/dl[b]	197 (173-223)	195 (171-221)	199 (176-227)	<0.001	195 (171-221)	200 (176-228)	<0.001	195 (171-221)	200 (176-228)	<0.001
LDL-cholesterol, mg/dl[b]	116 (95-139)	115 (94-138)	118 (96-141)	<0.001	115 (94-138)	118 (96-142)	<0.001	115 (94-138)	118 (96-142)	<0.001
HDL-cholesterol, mg/dl[b]	52 (44-61)	53 (46-63)	48 (42-57)	<0.001	54 (46-64)	48 (42-57)	<0.001	53 (46-63)	48 (42-57)	<0.001
Triglycerides, mg/dl[b]	106 (77-151)	97 (71-136)	125 (90-178)	<0.001	95 (70-132)	131 (96-186)	<0.001	97 (71-135)	128 (93-181)	<0.001
HOMA-IR[b]	2.48 (1.61-3.83)	2.13 (1.45-3.20)	3.40 (2.24-4.96)	<0.001	2.06 (1.42-3.05)	3.60 (2.46-5.16)	<0.001	2.11 (1.44-3.17)	3.49 (2.34-5.06)	<0.001
AST, IU/L[b]	24 (20-28)	23 (20-28)	24 (20-29)	<0.001	23 (20-27)	25 (21-30)	<0.001	23 (20-27)	24 (20-29)	<0.001
ALT, IU/L[b]	23 (18-32)	22 (17-30)	27 (20-37)	<0.001	22 (17-29)	28 (21-39)	<0.001	22 (17-29)	27 (20-37)	<0.001
GGT, IU/L[b]	26 (18-41)	24 (17-38)	30 (21-45)	<0.001	23 (16-36)	32 (22-50)	<0.001	24 (17-38)	30 (22-46)	<0.001
Platelet count, x10^9/mm^3[b]	235 (201-272)	233 (199-269)	238 (204-276)	<0.001	234 (200-270)	237 (203-275)	0.002	233 (199-269)	238 (205-277)	<0.001

Comparison between independent groups were performed by Mann-Whitney and Chi-square test for quantitative and categorical variables, respectively. Absence of excessive alcohol consumption: <140 g/week for women and <210 g/week for men. Metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; GGT, gamma-glutamyltransferase; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; WC, waist circumference.

[a]Data expressed as n (%).

[b]Data expressed as median (IQR).

validation of biomarkers to potentially replace liver biopsy in clinical trials.

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Conflict of interest

The authors have nothing to disclosure.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Hugo Perazzo: study concept and design; statistical analysis, interpretation of data; drafting and critical revision of the manuscript; Antonio Guilherme Pacheco, Raphael Gracindo and Alessandra Carvalho Goulart: data extraction, interpretation of data and critical revision of the manuscript; Maria de Jesus Mendes da Fonseca and Rosane Härter Griep: ELSA-Brasil study supervision; interpretation of data and critical revision of the manuscript.

Supplementary data

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