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RESEARCH ARTICLE

MAFLD and glomerular hyperfiltration in subjects with normoglycemia, prediabetes and type 2 diabetes: A cross-sectional population study

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Abstract

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD, 2020 diagnostic criteria) and glomerular hyperfiltration share common risk factors, including obesity, insulin resistance, impaired glucose tolerance, diabetes, dyslipidemia, and hypertension.

Aims: To assess the prevalence of MAFLD and its association with glomerular hyperfiltration and age-related worsening of kidney function in subjects with normoglycemia, prediabetes and type 2 diabetes mellitus (T2DM).

Methods: We analysed data recorded during occupational health visits of 125,070 Spanish civil servants aged 18–65 years with a de-indexed glomerular filtration rate (GFR) estimated with the chronic-kidney-disease-epidemiological (CKD-EPI) equation (estimated glomerular filtration rate [eGFR]) ≥60 mL/min. Subjects were categorised according to fasting plasma glucose levels <100 mg/dL (normoglycemia), ≥100 and ≤ 125 mg/dL (prediabetes), or ≥126 mg/dL and/or antidiabetic treatment (T2DM). The association between MAFLD and glomerular hyperfiltration, defined as a de-indexed eGFR above the age- and gender-specific 95th percentile, was assessed by multivariable logistic regression.

Results: In the whole study group, MAFLD prevalence averaged 19.3%. The prevalence progressively increased from 14.7% to 33.2% and to 48.9% in subjects with normoglycemia, prediabetes and T2DM, respectively ($p < 0.001$ for trend). Adjusted odds ratio (95% CI) for the association between MAFLD and hyperfiltration was 9.06 (8.53–9.62) in the study group considered as a whole, and 8.60 (8.03–9.21), 9.52 (8.11–11.18) and 8.31 (6.70–10.30) in subjects with normoglycemia, prediabetes and T2DM considered separately. In stratified analyses, MAFLD amplified age-dependent eGFR decline in all groups ($p < 0.001$).

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Conclusions: MAFLD prevalence increases across the glycaemic spectrum. MAFLD is significantly associated with hyperfiltration and amplifies the age-related eGFR decline.

KEYWORDS
hyperfiltration, MAFLD, normoglycemia, obesity, prediabetes, type 2 diabetes

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a multisystem disease with hepatic and extrahepatic involvement.[1] The relationship between NAFLD and glucose abnormalities is bidirectional.[1–3] Type 2 diabetes (T2DM) is a major risk factor for the development of NAFLD and its progression to advanced fibrosis.[2–4] In turn, NAFLD is associated with a 2.2-fold increased incidence of diabetes.[5] Moreover, the prevalence of NAFLD increases across the glycaemic spectrum and is positively associated with increased fasting plasma glucose (FPG) levels in nondiabetic individuals, independent of risk factors for T2DM, such as increasing age and body mass index (BMI).[6] The presence and the severity of NAFLD are strongly associated with the increased risk and severity of chronic kidney disease (CKD),[1] which is a common, frequently under-recognized condition, and a major risk factor for kidney failure and cardiovascular disease (CVD) in both diabetic and non-diabetic individuals. Moreover, in children and adults with the metabolic syndrome, NAFLD is associated with glomerular hyperfiltration,[7,8] which is a well-established pathogenic factor for accelerated renal function loss in subjects with obesity, diabetes and/or CKD,[9,10] and predicts all-cause mortality even in apparently healthy populations.[11] On the other hand, glomerular hyperfiltration is associated with an increased risk of NAFLD and liver fibrosis even in healthy adults.[12]

In early 2020, the term NAFLD was replaced by the term "metabolic dysfunction-associated fatty liver disease" (MAFLD) to better highlight the contribution of systemic metabolic dysregulation in the pathogenesis of NAFLD, beyond its histopathological similarities to alcohol-related liver disease.[13] Indeed, MAFLD is a disease-entity that—unlike NAFLD—in addition to fatty liver disorders, encompasses at least one of the following three criteria: overweight/obesity, T2DM, or two or more metabolic dysregulations in lean/normal weight subjects.[13] Since its introduction, more than 800 papers focusing on the mechanisms and epidemiology of MAFLD have been published.[14] Data show that, consequent to the global epidemics of metabolic disorders related to obesity and T2DM,[13] the prevalence of MAFLD is rapidly increasing in parallel with that CVD and CKD.[15,16] In turn, MAFLD increases the risk and severity of CVD and CKD even more strongly than NAFLD both in individuals with or without diabetes.[17–19] Moreover, preliminary data show that MAFLD is also associated with glomerular hyperfiltration in subjects with T2DM[20] or prediabetes and visceral obesity.[21] Together, these two abnormalities might synergistically contribute to the pathogenesis of CKD in these populations. On the other hand, finding that MAFLD and glomerular hyperfiltration, in addition to obesity and diabetes, may share a large series of other metabolic and functional abnormalities such as insulin resistance, prediabetes, dyslipidemia, hypertension, and progressively worsening kidney function, strongly suggests that the two abnormalities could be sustained by common pathogenic mechanisms.[22–24]

On the basis of the aforementioned observations, in the present cross-sectional, population-based study, we aimed to investigate the prevalence of MAFLD and its association with glomerular hyperfiltration and age-related worsening of kidney function over a continuum of FPG levels in subjects with normoglycemia, prediabetes and T2DM.

2 | MATERIALS AND METHODS

2.1 | Study design, participants and ethics

This was a cross-sectional analysis of data collected during routine occupational health visits performed between January 2012 and December 2013 in the Spanish communities of the Balearic and Canary Islands. The database included 234,995 working adults employed in public administration, health care, or postal services. General clinical and demographic information was collected at the time of inclusion by trained medical examiners. The study protocol was approved by the Ethics Committee of Clinical Research of the Balearic Islands (reference number 1887). We selected 125,070 adult workers aged 18–65, with a de-indexed eGFR ≥60 mL/min. Individuals with CKD stages III–V, type 1 diabetes, current treatment with systemic steroids, active cancer, or a history of malignancy in the previous 5 years, and pregnant women were excluded. According to their FPG levels and consistent with the American Diabetes Association (ADA) diagnostic criteria,[25] subjects were categorised into three groups characterised by normoglycemia (FPG <100 mg/dL), prediabetes (FPG ≥100 and ≤ 125 mg/dL), or T2DM (FPG ≥126 mg/dL and/or concomitant antidiabetic treatment).

2.2 | Measurements and calculations

Anthropometric parameters were measured according to the International Standard for Anthropometric Assessment (ISAK) criteria.[26] Height was measured to the nearest 0.5 cm using a scale-mounted telescopic stadiometer (Seca 220, Seca GmbH, Hamburg, Germany)

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with participants barefooted and heads maintained in anatomical position. Body weight was measured to the nearest 0.1 kg using a mechanical column scale (Seca 700, Seca GmbH, Hamburg, Germany); BMI was calculated by the standard formula (kg/m^2). Waist circumference (WC) was measured in triplicate by a flexible steel tape (Lufkin Executive Thinline W606, Apex Tool Group, Texas, United States) midway between the last rib and the top of the iliac crest, with the participant standing upright with feet closer together and arms hanging freely at the sides. The average of the three consecutive measurements was recorded and used for statistical analysis.

Blood pressure was measured in triplicate, 1 min apart, by an automatic and calibrated sphygmomanometer (OMRON M3, OMRON Healthcare.) after a 10-min resting period in a seated position. The average of the three measurements was recorded and used for statistical analysis.

Venous blood samples were collected after a 12-h overnight fast from the antecubital vein in suitable vacutainers. Samples were centrifuged (15 min, 1000 g, 4°C), to obtain serum which was stored at −20°C and analysed for FPG, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and uric acid levels within 3 days in a centralised laboratory and by standard procedures, using an autoanalyzer (SYNCHRON CX®9 PRO, Beckman Coulter.).

The presence of hepatic steatosis was assessed by the validated Fatty Liver Index (FLI) equation proposed by Bedogni G et al.[27]: $FLI = (e^{0.953*\log e\ (\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e\ (\text{GGT}) + 0.053*\text{waist circumference} - 15.745})/(1 + e^{0.953*\log e\ (\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e\ (\text{GGT}) + 0.053*\text{waist circumference} - 15.745})* 100$.

Glomerular filtration rate (GFR) was estimated by the 2009 CKD-EPI equation[28] and de-indexed for body surface area (BSA) to avoid GFR underestimation in patients with overweight/obesity by the formula: eGFR mL/min = (eGFR mL/min/1.73 m^2 * BSA)/1.73 m^2.[29] Body surface area was calculated by the DuBois and DuBois equation.[30]

Definitions According to the 2020 International Expert Consensus Statement,[13] MAFLD was defined as the presence of steatosis—as assessed by the FLI equation[27] with a cut-off value of ruling-in hepatic steatosis of ≥60—in combination with at least one of the following clinical features: (1) overweight/obesity; (2) T2DM; (3) metabolic dysregulation in lean/normal weight subjects. Metabolic dysregulation was defined as the combination of at least two of the followings: (1) WC ≥ 102 cm in men and ≥88 cm in women; (2) Blood pressure ≥130/85 mmHg and/or blood pressure-lowering drug treatment; (3) Plasma triglyceride levels ≥150 mg/dL (≥1.70 mmol/L) and/or lipid-lowering drug treatment; (4) Plasma High Density Level Cholesterol (HDL-C) levels <40 mg/dl (<1.0 mmol/L) in men and <50 mg/dl (<1.3 mmol/L) in women or lipid-lowering drug treatment; (5) Prediabetes; (6) Homoeostasis Model Assessment of Insulin Resistance (HOMA-IR) score ≥2.5; (7) Plasma C-reactive protein level more than 2 mg/L.

According to the World Health Organization criteria, overweight and obesity were defined by a BMI ≥25 and < 30 kg/m^2 and ≥30 kg/m^2, respectively.

Hypertension was defined as Systolic Blood Pressure (SBP) ≥130 mmHg and/or Diastolic Blood Pressure (DBP) ≥85 mmHg, or concomitant treatment with any blood pressure-lowering medication.[15,31] Glomerular hyperfiltration was defined as a de-indexed eGFR above the age- and gender-specific 95th percentile.[24]

2.3 | Statistical analyses

Variable distributions were assessed by using the Kolmogorov–Smirnov test. Continuous variables were expressed as means ± standard deviations (SD). Categorical variables were expressed as counts (%). Differences between the groups (normoglycemia, prediabetes, diabetes) were assessed by one-way analysis of variance or unequal variance *t*-test in case of heterogeneity for continuous variables, or by Chi-Square for categorical variables. Post hoc analyses were performed by applying the Bonferroni method. Differences between the subgroups (non-hyperfiltering, hyperfiltering) were assessed by independent sample *t*-test for continuous variables or by Chi-square test for categorical variables.

Odds ratios and corresponding 95% confidence intervals were calculated by multivariate logistic regression to assess the association between MAFLD and glomerular hyperfiltration for each group. Specifically, logistic regression was adjusted for age and sex (multivariable Model 1), and for age, sex, smoking habit, and use of antihypertensive and lipid-lowering medications (multivariable Model 2).

Finally, to test the possible interaction effect between MAFLD and age on eGFR, adjusted for sex, a multiple linear regression analysis was carried out, including the interaction term (MAFLD *x* age), for each group. A stratified analysis was then carried out for subjects with and without MAFLD.

All statistical tests were two-sided, and p values < 0.05 were considered statistically significant. Statistical analyses were conducted using the Statistical Package for the Social Sciences version 26.0 (IBM Company).

3 | RESULTS

Of the 125,070 subjects fulfilling the selection criteria, 60.0% were males and 33.1% were current smokers. Age averaged 40.0 ± 10.7 years. MAFLD affected 24,112 (19.3%) subjects, and 6249 (5.0%) were hyperfiltrating. Mean BMI was 26.1 ± 4.7 kg/m^2, 17.9% participants were obese, and 36.0% were overweight (Table 1). Hyperfiltration was observed in 3511 (14.6%) participants with MAFLD and in 2738 (2.7%) without MAFLD (p < 0.001). (Table S1).

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3.1 | Subject characteristics according to glycaemic status

Diabetes and prediabetes were more frequent among male subjects. Among male subjects (n = 75,015), 16.7% had prediabetes and 7.2% had diabetes, while among female subjects (n = 50,055), 9.2% had prediabetes and 4% had diabetes. As shown in Table 1, across the study groups, there was a significant increase in age, prevalence of MAFLD and former smokers, FLI, BMI, prevalence of obesity, WC in both sexes, SBP, DBP, mean arterial pressure (MAP), presence of arterial hypertension, triglycerides, ALT, AST, GGT levels, and use of antihypertensive and lipid lowing therapies (p < 0.001 for all

TABLE 1 Characteristics of the study population overall and according to glycaemic status.

	Overall	Normoglycemia	Prediabetes	Diabetes	*p*-value
n (%)	125,070	100,537 (80.4)	17,156 (13.7)	7377 (5.9)	
Gender (males), *n* (%)	75,015 (60.0)	57,092 (56.8)	12,534 (73.1)	5389 (73.1)	<0.001[a,c]
Age (years)	40.0 ± 10.7	38.4 ± 10.2	44.9 ± 9.9	50.5 ± 8.6	<0.001[a,b,c]
Smoking status, *n* (%)					<0.001
Never	21,051 (16.8)	51,737 (51.5)	7810 (45.5)	3052 (41.4)	a,b,c
Former	62,599 (50.1)	15,103 (15.0)	3787 (22.1)	2161 (29.3)	a,b,c
Current	41,420 (33.1)	33,697 (33.5)	5559 (32.40)	2164 (29.3)	a,b,c
BMI (kg/m^2)	26.1 ± 4.7	25.5 ± 4.5	27.8 ± 4.9	29.7 ± 5.3	<0.001[a,b,c]
BMI categories, *n* (%)					<0.001
BMI <25 kg/m^2	57,665 (46.1)	51,323 (51.0)	4999 (29.1)	1343 (18.2)	a,b,c
BMI 25–29 kg/m^2	44,995 (36.0)	34,799 (34.6)	7373 (43.0)	2823 (38.3)	a,b,c
BMI ≥30 kg/m^2	22,410 (17.9)	14,415 (14.3)	4784 (27.9)	3211 (43.5)	a,b,c
WC in men (cm)	88.8 ± 8.7	88.0 ± 8.5	90.4 ± 8.6	92.7 ± 8.9	<0.001[a,b,c]
WC in women (cm)	76.1 ± 7.3	75.7 ± 7.1	78.5 ± 7.7	80.1 ± 7.5	<0.001[a,b,c]
SBP (mmHg)	123.5 ± 16.2	121.7 ± 15.4	128.3 ± 16.8	136.3 ± 18.2	<0.001[a,b,c]
DBP (mmHg)	75.1 ± 11.0	73.9 ± 10.5	78.6 ± 11.0	83.0 ± 11.3	<0.001[a,b,c]
MAP	91.2 ± 11.7	89.9 ± 11.1	95.2 ± 12.0	100.8 ± 12.5	<0.001[a,b,c]
Hypertension, *n* (%)	30,354 (24.3)	19,525 (19.4)	6249 (36.4)	4580 (62.1)	<0.001[a,b,c]
FPG (mg/dL)	91.0 ± 18.7	85.5 ± 7.9	106.4 ± 5.9	129.7 ± 50.5	<0.001[a,b,c]
Total cholesterol (mg/dL)	190.2 ± 36.8	187.3 ± 36.0	202.3 ± 37.8	201.1 ± 37.5	<0.001[a,c]
LDL-C (mg/dL)[d]	117.8 ± 43.0	115.6 ± 39.3	128.0 ± 50.3	125.6 ± 63.9	<0.001[a,c]
HDL-C (mg/dL)[d]	56.4 ± 11.1	57.1 ± 11.0	53.5 ± 10.8	52.4 ± 10.8	<0.001[a,c]
Triglycerides (mg/dL)	113.6 ± 80.3	105.6 ± 64.9	139.0 ± 106.4	162.3 ± 145.0	<0.001[a,b,c]
Uric acid (mg/dL)[e]	4.9 ± 1.3	4.8 ± 1.3	5.3 ± 1.3	5.3 ± 1.4	<0.001[a,c]
ALT (IU/L)[f]	29.0 ± 19.2	28.1 ± 18.4	32.0 ± 20.6	35.3 ± 23.2	<0.001[a,b,c]
AST (IU/L)[g]	20.9 ± 12.5	20.3 ± 12.1	23.1 ± 14.1	24.2 ± 14.4	<0.001[a,b,c]
GGT (IU/L)	31.0 ± 38.3	28.4 ± 32.0	38.7 ± 52.1	47.6 ± 63.4	<0.001[a,b,c]
FLI	32.4 ± 26.8	28.7 ± 24.9	44.6 ± 28.3	55.6 ± 28.4	<0.001[a,b,c]
MAFLD, *n* (%)	24,112 (19.3)	14,809 (14.7)	5697 (33.2)	3606 (48.9)	<0.001[a,b,c]
Serum creatinine (mL/dL)	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	<0.001[a,b,c]
eGFR (mL/min)	110.5 ± 20.6	111.1 ± 20.6	108.5 ± 20.6	108.3 ± 20.4	<0.001[a,c]
Hyperfiltration, *n* (%)	6249 (5.0)	4553 (4.5)	978 (5.7)	718 (9.7)	<0.001[a,b,c]
Therapies, *n* (%)					
Anti-hypertensive	8622 (6.9)	4671 (4.6)	1925 (11.2)	2026 (27.5)	<0.001[a,b,c]

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TABLE 1 (Continued)

	Overall	Normoglycemia	Prediabetes	Diabetes	*p*-value
Glucose-lowering	5315 (4.2)	0 (0.0)	0 (0.0)	5315 (72.0)	<0.001[a,b]
Lipid-lowering	3296 (2.6)	1901 (1.9)	769 (4.5)	626 (8.5)	<0.001[a,b,c]

Note: Data are mean ± SD and number (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MAP, mean arterial pressure; SBP, systolic blood pressure; WC, Waist circumference.

[a]Significant difference between normoglycemia and diabetes.

[b]Significant difference between prediabetes and diabetes.

[c]Significant difference between normoglycemia and prediabetes.

[d]LDL-C and HDL-C available for $n = 30,102$ (normoglycemia $n = 24,299$; prediabetes $n = 3996$; diabetes $n = 1807$).

[e]Uric acid available for $n = 82,099$ (normoglycemia $n = 66,775$; prediabetes $n = 10,659$; diabetes $n = 4665$).

[f]ALT available for $n = 125,020$ (normoglycemia $n = 100,512$; prediabetes $n = 17,145$; diabetes $n = 7363$).

[g]AST available for $n = 26,566$ (normoglycemia $n = 21,885$; prediabetes $n = 3352$; diabetes $n = 1329$).

p-values obtained by one-way ANOVA for continuous variables or by Chi-Square for categorical variables. Post-hoc test by Bonferroni.

considered parameters). Conversely, the prevalence of subjects with normal weight significantly decreased across the three groups. Similarly, the proportion of never and current smokers also significantly decreased from normoglycemia to T2DM. The prevalence of overweight subjects was significantly different across groups and was highest in the prediabetes group. The prediabetes and diabetes groups presented higher values of total cholesterol, LDL-C, and uric acid, and lower levels of HDL-C than the normoglycemia group. The estimated GFR was similar in the prediabetes and diabetes groups and significantly lower in these two groups than in the normoglycemia group. The proportion of subjects with hyperfiltration significantly increased across the groups from 4.5% to 5.7% and to 9.7% in subjects with normoglycemia, prediabetes and T2DM, respectively ($p < 0.001$ for all comparisons; $p < 0.001$ for trend).

3.2 | Subjects characteristics according to glycaemic status and presence or absence of hyperfiltration

Hyperfiltration was more frequent in females than in males in the prediabetes and diabetes groups. Within the prediabetes group, hyperfiltration was present in 7.3% of females versus 5.1% of males. Within the diabetes group, hyperfiltration was present in 11.4% of females versus 9.1% of males. As shown in Table 2, in the normoglycemia and prediabetes groups, hyperfiltering subjects were more frequently never smokers and less frequently current smokers than non-hyperfiltering subjects, whereas in the diabetes group, smoking habit was similar in hyperfiltering and non-hyperfiltering subjects. In all three groups, hyperfiltering subjects were younger, had higher BMI, lower prevalence of normal weight and overweight, higher prevalence of obesity, higher WC in both sexes, higher FLI values, higher prevalence of MAFLD, higher SBP, DBP, MAP, FPG, triglycerides, and lower serum creatinine as compared to non-hyperfiltering. Presence of hypertension and antihypertensive treatment were higher in hyperfiltering than in non-hyperfiltering participants for the normoglycemia and prediabetes groups, whereas ALT was higher in hyperfiltering than in non-hyperfiltering subjects for the prediabetes and diabetes groups. AST and GGT were higher in the hyperfiltering subgroup for diabetes subjects only, and there were no differences in total and HDL-C between hyperfiltering and non-hyperfiltering subjects in any of the three groups. The frequency of lipid-lowering treatment was higher in non-hyperfiltering subjects in the normoglycemia and diabetes groups. In the normoglycemia group only, LDL-C was higher in non-hyperfiltering than in hyperfiltering subjects and uric acid differed although its value was numerically identical. Finally, both in hyperfiltering and in non-hyperfiltering subjects across the three glycaemic groups, eGFR was always significantly higher in subjects with MAFLD than in those without MAFLD (Figure 1, Panels A, B and C; Figure S1, Panels A and B). Comparisons between hyperfiltering subjects across the glycaemic groups are presented in Table 2.

3.3 | Predicting hyperfiltration in the normoglycemia, prediabetes, and T2DM groups

The multivariable logistic regression models adjusted for age and sex (Model 1) and for age, sex, smoking status, and therapy with antihypertensive and lipid-lowering medications (Model 2), showed that MAFLD was independently and significantly associated with hyperfiltration along with younger age and male sex in the study group considered as a whole, as well as in subjects with normoglycemia, prediabetes and T2DM considered separately (Table 3).

A linear regression of the whole sample showed an independent positive association between eGFR and BMI, DBP and HDL-C, and an independent negative association between eGFR and age, sex (male vs. female), triglycerides and GGT (Table S3).

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TABLE 2 Characteristics of the study population according to glycaemic status and presence of hyperfiltration.

	Normoglycaemia (n = 100,537)			Prediabetes (n = 17,156)			Diabetes (n = 7377)			
	Non-hyperfiltering	Hyperfiltering	p^*	Non-hyperfiltering	Hyperfiltering	p^*	Non-hyperfiltering	Hyperfiltering	p^*	p^{**}
n (%)	95,984 (95.5)	4553 (4.5)		16,178 (94.3)	978 (5.7)		6659 (90.3)	718 (9.7)		
Gender (males), n (%)	54,477 (56.80)	2615 (57.40)	0.367	11,892 (73.50)	642 (65.60)	<0.001	4897 (73.50)	492 (68.50)	0.004	<0.001[a,c]
Age (years)	38.4 ± 10.2	36.9 ± 9.9	<0.001	45.0 ± 9.9	43.1 ± 9.7	<0.001	50.7 ± 8.6	48.0 ± 8.7	<0.001	<0.001[a,b,c]
Smoking status, n (%)			<0.001			0.018			0.058	<0.001[a,c]
Never	49,160 (51.20)	2577 (56.60)[d]		7334 (45.30)	476 (48.70)[d]		2728 (41.00)	324 (45.10)		
Former	14,400 (15.00)	703 (15.40)		3562 (22.00)	225 (23.00)		1954 (29.30)	207 (28.80)		
Current	32,424 (33.80)	1273 (28.00)[d]		5282 (32.60)	277 (28.30)[d]		1977 (29.70)	187 (26.00)		
BMI (kg/m^2)	25.2 ± 4.1	32.2 ± 5.9	<0.001	27.4 ± 4.4	35.0 ± 6.2	<0.001	29.0 ± 4.8	35.9 ± 5.6	<0.001	<0.001[a,b,c]
BMI categories, n (%)			<0.001			<0.001			<0.001	<0.001[a,b,c]
BMI <25 kg/m^2	50,903 (53.0)	420 (9.2)[d]		4977 (30.8)	22 (2.2)[d]		1335 (20.0)	8 (1.1)[d]		
BMI 25–29 kg/m^2	33,396 (34.80)	1403 (30.80)[d]		7174 (44.30)	199 (20.30)[d]		2744 (41.20)	79 (11.00)[d]		
BMI ≥30 kg/m^2	11,685 (12.20)	2730 (60.00)[d]		4027 (24.90)	757 (77.40)[d]		2580 (38.70)	631 (87.90)[d]		
Waist circumference in men (cm)	87.56 ± 8.18	97.95 ± 9.01	<0.001	89.9 ± 8.3	101.1 ± 8.2	0.019	91.7 ± 8.3	102.5 ± 8.2	0.027	<0.001[a,b,c]
Waist circumference in women (cm)	75.12 ± 6.69	87.12 ± 6.03	<0.001	77.7 ± 7.4	88.4 ± 5.1	<0.001	79.0 ± 7.2	88.1 ± 4.4	<0.001	<0.001[a,c]
SBP (mmHg)	121.5 ± 15.3	126.6 ± 16.0	<0.001	128.0 ± 16.7	133.4 ± 18.1	<0.001	136.1 ± 18.1	138.7 ± 19.1	<0.001	<0.001[a,b,c]
DBP (mmHg)	73.8 ± 10.5	77.3 ± 11.0	<0.001	78.4 ± 11.0	82.1 ± 11.0	<0.001	82.7 ± 11.2	85.3 ± 11.7	<0.001	<0.001[a,b,c]
MAP	89.7 ± 11.1	93.7 ± 11.5	<0.001	94.9 ± 11.9	99.2 ± 12.3	<0.001	100.5 ± 12.4	103.1 ± 13.0	<0.001	<0.001[a,b,c]
Hypertension, n (%)	18,150 (18.90)	1375 (30.20)	<0.001	5747 (35.50)	502 (51.30)	<0.001	4116 (61.80)	464 (64.60)	0.140	<0.001[a,b,c]
FPG (mg/dL)	85.4 ± 7.9	86.8 ± 7.8	<0.001	106.4 ± 5.9	107.0 ± 6.3	0.001	129.1 ± 50.1	135.9 ± 53.4	0.001	<0.001[a,b,c]
Total cholesterol (mg/dL)	187.3 ± 36.1	187.3 ± 33.6	0.999	202.4 ± 38.0	200.8 ± 35.7	0.204	200.9 ± 37.4	202.9 ± 38.2	0.192	<0.001[a,b,c]
LDL-C (mg/dL)[g]	115.9 ± 39.4	111.0 ± 37.1	<0.001	128.5 ± 50.7	122.9 ± 46.3	0.051	125.7 ± 64.6	124.8 ± 59.3	0.845	<0.001[a,c]
HDL-C (mg/dL)[g]	57.1 ± 11.2	56.8 ± 8.3	0.223	53.5 ± 10.9	53.4 ± 9.5	0.790	52.5 ± 11.0	51.6 ± 9.3	0.255	<0.001[a,c]
Triglycerides (mg/dL)	105.1 ± 65.0	116.6 ± 60.9	<0.001	138.4 ± 106.6	149.7 ± 101.1	0.001	161.2 ± 145.0	172.8 ± 145.3	0.041	<0.001[a,b,c]
Uric acid (mg/dL)[h]	4.8 ± 1.3	4.8 ± 1.3	0.019	5.3 ± 1.3	5.4 ± 1.3	0.240	5.3 ± 1.4	5.4 ± 1.4	0.527	<0.001[a,c]
ALT (IU/L)[e]	28.1 ± 18.4	28.1 ± 18.3	0.863	31.9 ± 20.6	34.0 ± 19.7	0.002	35.0 ± 22.4	37.9 ± 29.5	0.001	<0.001[a,b,c]
AST (IU/L)[f]	20.3 ± 12.3	20.5 ± 9.7	0.593	22.9 ± 14.2	24.3 ± 12.7	0.083	23.7 ± 14.2	26.9 ± 15.3	0.003	<0.001[a,b,c]
GGT (IU/L)	28.4 ± 32.2	29.0 ± 27.8	0.239	38.6 ± 52.8	39.8 ± 38.7	0.486	46.9 ± 57.8	54.0 ± 101.7	0.004	<0.001[a,b,c]
FLI	27.4 ± 24.1	56.1 ± 26.8	<0.001	42.9 ± 27.7	72.3 ± 22.8	<0.001	53.2 ± 28.0	78.4 ± 19.8	<0.001	<0.001[a,b,c]

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TABLE 2 (Continued)

	Normoglycaemia (n = 100,537)			Prediabetes (n = 17,156)			Diabetes (n = 7377)			
	Non-hyperfiltering	Hyperfiltering	p^*	Non-hyperfiltering	Hyperfiltering	p^*	Non-hyperfiltering	Hyperfiltering	p^*	p^{**}
MAFLD, n (%)	12,615 (13.1)	2194 (48.2)	<0.001	4974 (30.7)	723 (73.9)	<0.001	3012 (45.2)	594 (82.7)	<0.001	<0.001[a,b,c]
Serum creatinine (mL/dL)	0.8 ± 0.2	0.6 ± 0.1	<0.001	0.9 ± 0.2	0.7 ± 0.1	<0.001	0.9 ± 0.2	0.7 ± 0.1	<0.001	<0.001[a,b,c]
eGFR (mL/min)	109.2 ± 18.8	150.4 ± 17.9	<0.001	106.3 ± 18.6	145.3 ± 16.8	<0.001	104.8 ± 17.6	140.8 ± 16.4	<0.001	<0.001[a,b,c]
Anti-hypertensive therapy, n (%)	4394 (4.6)	277 (6.1)	<0.001	1784 (11.0)	141 (14.4)	0.001	1844 (27.7)	182 (25.3)	0.181	<0.001[a,b,c]
Glucose-lowering therapy, n (%)	0.0 (0.0)	0.0 (0.0)		0.0 (0.0)	0.0 (0.0)		4820 (72.4)	495 (68.9)	0.151	-
Lipid-lowering therapy, n (%)	1834 (1.9)	67 (1.5)	0.034	724 (4.5)	45 (4.6)	0.853	580 (8.7)	46 (6.4)	0.035	<0.001[a,c]

Note: Data are mean ± SD and number (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MAP, mean arterial pressure; SBP, systolic blood pressure.

[a]Significant difference between hyperfiltering-normoglycemia and hyperfiltering-prediabetes.

[b]Significant difference between hyperfiltering-prediabetes and hyperfiltering-diabetes.

[c]Significant difference between hyperfiltering-normoglycemia and hyperfiltering-diabetes.

[d]Significant difference between paired categories.

[e]ALT available for n = 125,020 (normoglycemia n = 100,512; prediabetes n = 17,145; diabetes n = 7363).

[f]AST available for n = 26,566 (normoglycemia n = 21,885; prediabetes n = 3352; diabetes n = 1329).

[g]LDL-C and HDL-C available for n = 30,102 (normoglycemia n = 24,299; prediabetes n = 3996; diabetes n = 1807).

[h]Uric acid available for n = 82,099 (normoglycemia n = 66,775; prediabetes n = 10,659; diabetes n = 4665).

*p-values obtained by independent t-test for continuous variables or by Chi-Square for categorical variables between the non-hyperfiltering and hyperfiltering groups for each category of glycaemic status, separately.

**p-values obtained by one-way ANOVA for continuous variables or Chi-Square for categorical variables between the three hyperfiltering groups. Post-hoc test by Bonferroni.

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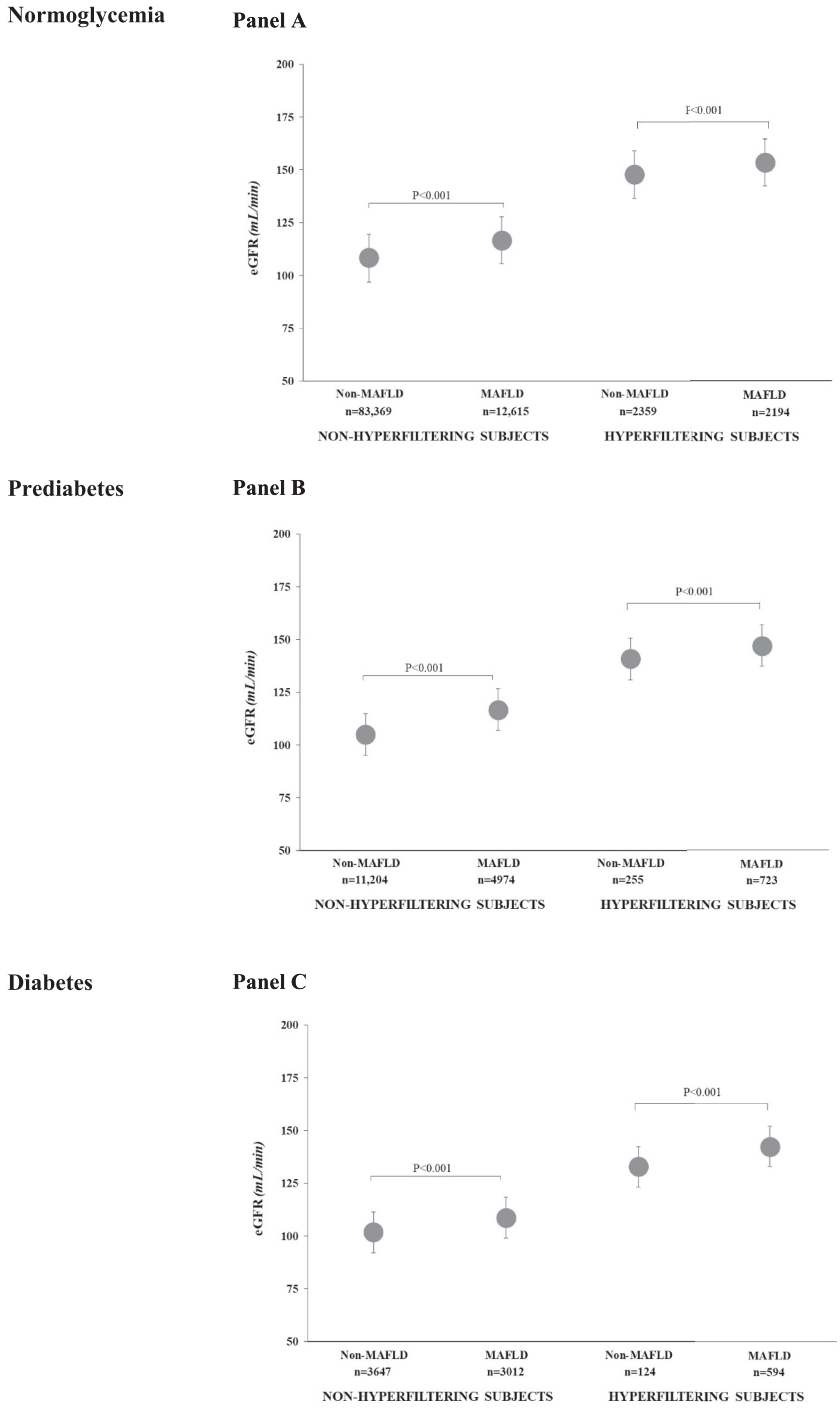

FIGURE 1 Distribution of estimated glomerular filtration rate (eGFR) in non-hyperfiltering and hyperfiltering subjects according to the presence or absence of MAFLD (MAFLD, non-MAFLD) for normoglycemia, prediabetes, and diabetes ($p < 0.001$). Number of patients per group: normoglycemia (non-hyperfiltering: non-MAFLD $n = 83,369$; MAFLD $n = 12,615$; hyperfiltering: non-MAFLD $n = 2359$; MAFLD $n = 2194$); prediabetes (non-hyperfiltering: non-MAFLD $n = 11,204$; MAFLD $n = 4974$; hyperfiltering: non-MAFLD $n = 255$; MAFLD $n = 723$); diabetes (non-hyperfiltering: non-MAFLD $n = 3647$; MAFLD $n = 3012$; hyperfiltering: non-MAFLD $n = 124$; MAFLD $n = 594$).

3.4 | Age-declining eGFR in subjects with and without MAFLD according to glycaemic status

Mean eGFR declined in parallel with increasing age categories and was consistently and significantly higher in subjects with MAFLD than in those without (Figure 2). Furthermore, the multiple linear regression model considering MAFLD, age, and their interaction term, adjusted for sex. (Table S2, Model 2 for each group separately), revealed that the effect of age on eGFR was modified by the presence of MAFLD ($p < 0.001$). In stratified data analyses according to the presence or absence of MAFLD, the effect of age on eGFR decline was amplified by the presence of MAFLD in each of the three groups ($p < 0.001$) (Table S2). In every group, the eGFR difference between subjects with and without MAFLD tended to decrease across increasing age categories, independently of potential confounders (Figure 2, Panels A, B, C), and according to presence or absence of hyperfiltration (Figure S2, Panels A-1, A-2, B-1, B-2, C-1, C-2).

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TABLE 3 Univariate (crude) and multivariable (adjusted) logistic regression derived Odds ratio (OR) and 95% confidence intervals (CI) for hyperfiltration for the whole sample and in subjects with normoglycemia, prediabetes and diabetes.

	Univariate		Multivariable				
				Model 1		Model 2	
	OR (95% CI)	*p*		OR (95% CI)	*p*	OR (95% CI)	*p*
Overall							
MAFLD	6.11 (5.80; 6.44)	<0.001	MAFLD	9.14 (8.61; 9.70)	<0.001	9.06 (8.53; 9.62)	<0.001
			Age (y)	0.97 (0.97; 0.97)	<0.001	0.97 (0.97; 0.97)	<0.001
			Male versus female	1.94 (1.83; 2.06)	<0.001	1.91 (1.78; 2.02)	<0.001
Normoglycemia							
MAFLD	6.18 (5.81; 6.57)	<0.001	MAFLD	8.65 (8.07; 9.26)	<0.001	8.60 (8.03; 9.21)	<0.001
			Age (y)	0.97 (0.97; 0.97)	<0.001	0.97 (0.97; 0.97)	<0.001
			Male versus female	1.75 (1.64; 1.88)	<0.001	1.72 (1.61; 1.84)	<0.001
Prediabetes							
MAFLD	6.40 (5.52; 7.41)	<0.001	MAFLD	9.66 (8.24; 11.34)	<0.001	9.52 (8.11; 11.18)	<0.001
			Age (y)	0.97 (0.96; 0.97)	<0.001	0.96 (0.96; 0.97)	<0.001
			Male versus female	2.93 (2.51; 3.41)	<0.001	2.89 (2.48; 3.67)	<0.001
Diabetes							
MAFLD	5.83 (4.77; 7.11)	<0.001	MAFLD	8.23 (6.64; 10.19)	<0.001	8.31 (6.70; 10.30)	<0.001
			Age (y)	0.96 (0.95; 0.96)	<0.001	0.96 (0.95; 0.97)	<0.001
			Male versus female	2.31 (1.92; 2.78)	<0.001	2.28 (1.89; 2.75)	<0.001

Note: Model 2 was adjusted for smoking status and use of antihypertensive and lipid lowering medications.

Abbreviations: CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; y, years.

4 | DISCUSSION

In this large population-based study, we found that the progressive increase in FPG levels in subjects with normoglycemia, prediabetes, or diabetes and preserved kidney function (de-indexed GFR ≥60 mL/min) was parallelled by a significant increase in the prevalence of MAFLD, which in turn was associated with an increasing prevalence of glomerular hyperfiltration. Notably, in each considered FPG subgroup, the prevalence of MAFLD was higher in hyperfiltering than in non-hyperfiltering subjects. In multivariable analyses, MAFLD was independently associated with glomerular hyperfiltration, even after adjusting for potentially confounding factors that may play a pathogenic role for both MAFLD and hyperfiltration (such as age, sex, and smoking habit), and use of blood pressure and lipid lowering medications that reflect the presence of risk factors like hypertension and dyslipidemia. Moreover, in patients with MAFLD, eGFR was uniformly higher than in those without MAFLD, and amplified the age-related eGFR decline in all groups.

The overall prevalence of MAFLD in our study population (19.3%), is lower than the prevalence of NAFLD reported globally (30.05%) and in Western Europe (25.1%) for the period 1990–2019.[32] Furthermore, the prevalence of MAFLD across the three glycaemic groups (14.7%, 33.2% and 48.9%) is also lower than the rates of NAFLD previously reported in individuals with normoglycemia in Japan (27%),[6] impaired FPG in the Tübingen Family and the TULIP studies (45%),[4] and diabetes (global prevalence 55%–75%).[33] These variations could be attributed to the differences in the diagnostic criteria for MAFLD and NAFLD,[13] and, possibly, to healthier food patterns that characterise diets in the Mediterranean regions.[34] Considering the known strong correlation of age with multiple major cardiometabolic risk factors, including MAFLD/NAFLD, it could be suggested that the younger mean age of our study population (40.0 ± 10.7 years) compared to the wider age range in previous studies may also contribute to the observed discrepancies.

Nevertheless, overall, over 50% of our subjects were overweight or obese, almost 20% had impaired FPG or T2DM, nearly 25% were hypertensive, and one-third were current smokers. Of concern, almost 15% of subjects with normal glucose metabolism, who were younger than subjects with prediabetes and diabetes, had MAFLD. Furthermore, almost 50% of them were overweight or obese, 20% had arterial hypertension, and one-third were current smokers. These findings are clinically relevant because even in a state of normoglycemia, the presence of hepatic steatosis is per se a risk factor for long-term hepatic and extra-hepatic complications.[35]

Finding that the prevalence of MAFLD progressively increases in subjects with normoglycemia, pre, or diabetes in parallel with the prevalence of glomerular hyperfiltration strongly corroborates the

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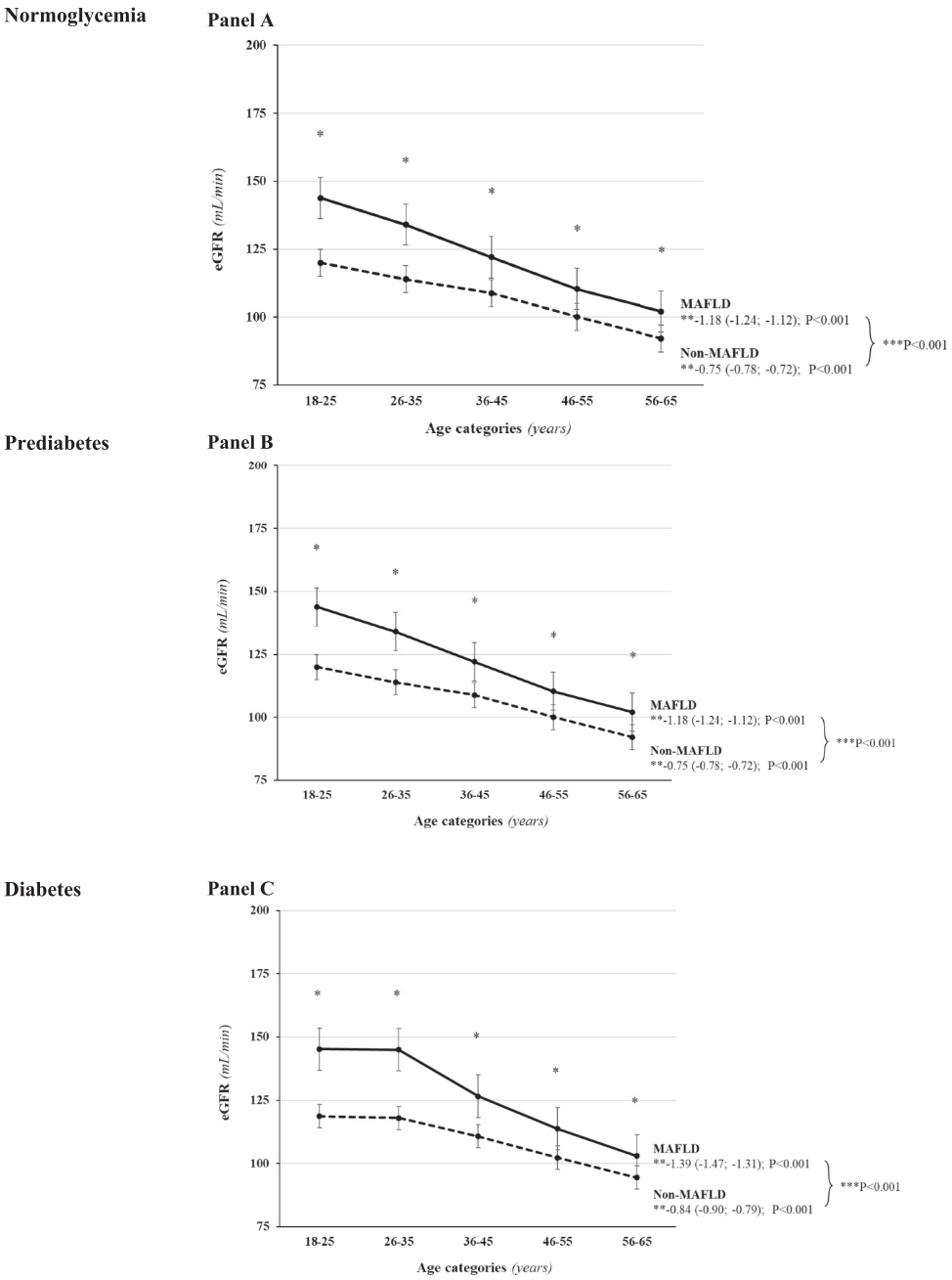

FIGURE 2 Mean and standard error of estimated glomerular filtration rate (eGFR) in subjects with and without MAFLD (MAFLD, Non-MAFLD) across age categories for normoglycemia (Panel A), prediabetes (Panel B), and diabetes (Panel C). *Significant difference between mean eGFR of MAFLD and non-MAFLD subjects for each age category by *T*-test analysis ($p < 0.001$); **Effect of age on eGFR decline in stratified analyses according to the presence or absence of MAFLD [β (95% CI)]; ***Multiple linear regression analyses with the effect of interaction term between MAFLD and age on eGFR ($p < 0.001$).

working hypothesis that the two abnormalities share common risk factors that progressively increase along the FPG continuum without any blood glucose threshold. Obesity could be the most relevant of these pathogenic factors as its prevalence increased across the studied groups and was more frequent in hyperfiltering than in non-hyperfiltering participants. Furthermore, finding that WC was larger in hyperfiltering than in non-hyperfiltering males and females is consistent with the evidence that lipolyticly active visceral fat plays a crucial role in the development of hyperfiltration.

However, one-fifth of the global NAFLD population is reported to be lean.[36] Notably, liver fat accumulation similarly predicts long-term hepatic and extrahepatic complications in lean and non-lean Caucasian subjects, regardless of their longitudinal progression to

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obesity and/or prevalence of PNPLA3 genetic variants predisposing to liver steatosis.[37]

This observation can be attributed to the fact that lean and obese subjects with NAFLD share similar features of insulin resistance and dyslipidemia.[38] Of note, even a small increase in liver fat is associated with hepatic and skeletal muscle insulin resistance, and further accumulation of liver fat beyond this relatively minimal threshold (~1.5% for hepatic insulin resistance and ~6% for muscle insulin resistance) is not associated with a more severe insulin resistance.[39]

Thus, insulin resistance-related hyperinsulinemia could be the common pathogenic factor for hyperfiltration in subjects with MAFLD as insulin might sustain glomerular hyperfiltration by enhancing tubular sodium reabsorption and exposing the macula densa to decreased sodium concentration. This results in tubule-glomerular feedback inhibition with preglomerular vasorelaxation leading to increased intraglomerular hydraulic pressure with consequent glomerular ultrafiltration.[40] The increased prevalence of markers of insulin resistance such as hypertriglyceridemia and hypertension in hyperfiltering subjects provides indirect evidence for the role of insulin resistance in the pathogenesis of glomerular hyperfiltration in this population. In addition, it could be suggested that the negative association of triglycerides and GGT with eGFR reflects the finding of a potentiating role of MAFLD on the age-related decline of eGFR. Overall, these results underscore the complexity of the interplay between cardiometabolic variables and kidney function regulation in the state of MAFLD.

Finding that, at multivariable analyses, male sex emerged as an independent risk factor for hyperfiltration is consistent with the evidence of a sex dimorphism in the epidemiology of T2DM, MAFLD, and CKD progression. However, this was inconsistent with the higher prevalence of hyperfiltering women compared to men in the prediabetes and diabetes groups, possibly indicating that the presence of a dysmetabolic state might affect women more than men with regard to kidney outcomes.

It is well documented that older age is a risk factor for T2DM, NAFLD, and CKD.[41] Consistently in our sample, FPG and MAFLD prevalence increased with increasing age in the three groups. Regarding renal function, the expected age-related decline of eGFR[42] was observed only between the normoglycemia versus the prediabetes and diabetes groups while the difference in eGFR between subjects with diabetes and prediabetes was masked by the higher prevalence of hyperfiltration in subjects with diabetes. Finding that younger age was associated with hyperfiltration is in line with the observation that hyperfiltering were younger than non-hyperfiltering subjects in each group, highlighting the role of vessel ageing in glomerular haemodynamic changes. Accordingly, younger arterioles, which are less affected by age-related vascular stiffness, are more responsive to vasodilation and vasoconstriction stimuli of various vasoactive, metabolic, hormonal, and pro-inflammatory factors. Moreover, within the limit of the cross-sectional design of the analyses, we found that the presence of MAFLD potentiated the age-related eGFR decline in every group which may be a result of the accelerated vessel ageing induced by the MAFLD-related metabolic disorders, consistent with data for diabetes-associated accelerated arterial ageing.[43]

Independent of the involved mechanisms, MAFLD-associated glomerular hyperfiltration per se may be a major pathogenic factor for GFR decline and CKD progression.[9] Thus, mitigation of MAFLD and its risk factors, could be instrumental in ameliorating glomerular hyperfiltration and limiting MAFLD-associated accelerated GFR decline.

4.1 | Limitations and strengths

This is an observational, cross-sectional study that does not allow establishing the temporality and causality of the association we found between MAFLD and hyperfiltration. The extremely large study population did not allow the use of gold standard procedures such as liver biopsy and/or ultrasound imaging for the diagnosis of MAFLD or the iohexol plasma clearance technique for the direct measurement of GFR,[44] which might have increased random data fluctuation and reduced the statistical power of the analyses. This limitation, however, is inherent to large population studies where relatively complex procedures cannot be applied to each participant. Conversely, the very large sample size largely offsets the limitations related to the use of suboptimal procedures to diagnose MAFLD and glomerular hyperfiltration and potentiates the statistical power of the analyses. Notably, the diagnostic and prognostic reliability of both FLI and CKD-EPI equations are generally considered acceptable for large-scale epidemiological studies.[13,45] Finally, the prevalence of MAFLD in our study could be underestimated due to the partial availability of key parameters such as C-reactive protein, Homoeostasis Model Assessment of Insulin Resistance, and HDL-C levels, that are essential for the diagnosis of MAFLD in lean subjects.

The major strength of the present study is the large sample size, representative of the average Caucasian population with preserved kidney function. To our knowledge, this is the first large-scale epidemiological study that specifically focuses on the recently defined entity of MAFLD, providing robust data on its prevalence and its strong and independent association with hyperfiltration across the whole glycaemic spectrum in the general population. Furthermore, underestimation of eGFR in patients with obesity was minimized by de-indexing eGFR for BSA.[29] In the absence of a universally accepted definition for hyperfiltration, we relied on an objective criterion such as eGFR values above the age- and sex-specific 95th.[24]

5 | CONCLUSIONS

In the general population of subjects with preserved kidney function, the prevalence of MAFLD increases across the glycaemic spectrum in parallel with the progressively increasing prevalence of glomerular hyperfiltration. The strong association we found between MAFLD and hyperfiltration at any glucose level conceivably suggests that these two abnormalities may share common and interconnected

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pathogenic mechanisms that could also contribute to the onset and progression of CKD. This could explain why the presence of MAFLD appeared to amplify the age-related eGFR decline. Longitudinal studies are needed to investigate whether and to what extent the presence of MAFLD is an independent risk factor for accelerated GFR decline (and possibly excess CVD risk) and whether sustained amelioration of MAFLD could translate into a substantial nephroprotection (and cardioprotection) in the long-term, even in the non-diabetic population.

AUTHOR CONTRIBUTIONS

Manuela Abbate and Aneliya Parvanova were involved in the conception and design of the study, the analysis and interpretations of data, and the drafting of the manuscript. Ángel Arturo López-González was involved in data collection and curation. Aina M. Yañez was involved in the conception and design of the study and in the analysis and interpretation of data. Miquel Bennasar-Veny was involved in the conception and design of the study. José Ignacio Ramírez-Manent was involved in data curation. Elia Reseghetti was involved in revising and editing the manuscript. Piero Ruggenenti was involved in the analysis and interpretation of data and in the critical revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The protocol conformed to the principles of Good Clinical Practice.

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PEER REVIEW

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