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ORIGINAL ARTICLE

Alcohol consumption and liver phenotype of individuals with alpha-1 antitrypsin deficiency

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Abstract

Background and Aims: Alpha-1 antitrypsin deficiency is an inherited disorder caused by alpha-1 antitrypsin (AAT) mutations. We analysed the association between alcohol intake and liver-related parameters in individuals with the heterozygous/homozygous Pi*Z AAT variant (Pi*MZ/Pi*ZZ genotype) found in the United Kingdom Biobank and the European Alpha1 liver consortium.

Methods: Reported alcohol consumption was evaluated in two cohorts: (i) the community-based United Kingdom Biobank (17 145 Pi*MZ, 141 Pi*ZZ subjects, and

Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CAP, controlled attenuation parameter; HSD17B13, 17β-hydroxysteroid dehydrogenase type 13 gene; LSM, liver stiffness measurements; Pi, protease inhibitor; Pi*M, normal AAT allele; Pi*MZ, AAT genotype with heterozygosity for the Pi*Z variant; Pi*S, mutant *SERPINA1* allele variant termed "S"; Pi*SZ, AAT genotype with compound heterozygosity for Pi*Z and Pi*S variant; Pi*Z, mutant *SERPINA1* allele variant termed "Z"; Pi*ZZ, AAT genotype with homozygosity for the Pi*Z variant; PNPLA3, patatin-like phospholipase domain-containing protein 3; *SERPINA1*, AAT gene; TE, transient elastography (FibroScan®); TM6SF2, transmembrane 6 superfamily member 2.

425 002 non-carriers [Pi*MM]); and (ii) the European Alpha1 liver consortium (561 Pi*ZZ individuals). Cohort (ii) included measurements of carbohydrate-deficient transferrin (CDT).

Results: In both cohorts, no/low alcohol intake was reported by >80% of individuals, while harmful consumption was rare (~1%). Among Pi*MM and Pi*MZ individuals from cohort (i), moderate alcohol consumption resulted in a <30% increased rate of elevated transaminases and ~50% increase in elevated gamma-glutamyl transferase values, while harmful alcohol intake led to an at least twofold increase in the abnormal levels. In Pi*ZZ individuals from both cohorts, moderate alcohol consumption had no marked impact on serum transaminase levels. Among Pi*ZZ subjects from cohort (ii) who reported no/low alcohol consumption, those with increased CDT levels more often had signs of advanced liver disease.

Conclusions: Pi*MZ/Pi*ZZ genotype does not seem to markedly aggravate the hepatic toxicity of moderate alcohol consumption. CDT values might be helpful to detect alcohol consumption in those with advanced fibrosis. More data are needed to evaluate the impact of harmful alcohol consumption.

KEYWORDS
alcohol, FibroScan, liver cirrhosis, liver fibrosis, Pi*Z, *SERPINA1*

1 | INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) arises from inherited mutations in the alpha-1 antitrypsin (AAT) gene with Pi*Z being the clinically most relevant one.[1–3] Pi*Z impairs the secretion of the hepatocyte-made protein. The consecutively decreased AAT serum levels predispose to lung emphysema while hepatic AAT accumulation confers proteotoxic stress. The majority of retained AAT becomes degraded, but about 15% polymerizes in the endoplasmic reticulum and forms inclusions that can be visualized immunohistochemically or via Periodic acid Schiff plus diastase (PAS-D) staining.[4,5]

The presence of homozygous Pi*Z variant, known as Pi*ZZ genotype, is found in 1:2000 Caucasians, while its heterozygous occurrence labelled Pi*MZ is seen in 1:30 subjects of European descent.[2] Cross-sectional examinations revealed significant liver fibrosis in 20–35% of Pi*ZZ individuals corresponding to a ~20 times increased lifetime risk of liver cirrhosis compared to the general population.[5–8] In contrast, Pi*MZ subjects carry only a twofold increased predisposition to advanced liver scarring, but this genetically conferred risk increases in the presence of additional hits.[7] While the liver phenotype in AATD subjects is highly variable and the disease modifiers are incompletely understood, known metabolic/nutritional co-factors such as the presence of obesity, metabolic syndrome, or diabetes as well as alcohol consumption have been proposed. With regard to the latest, subjects with Pi*MZ genotype and chronic alcohol misuse display a 2–6 times elevated risk of liver cirrhosis compared to drinkers without AAT mutation.[4,9,10] In contrast, the impact of moderate alcohol consumption as well as the impact of alcohol in Pi*ZZ individuals remains to be systematically examined.

Key points

We studied the impact of alcohol consumption on liver-related parameters in individuals with alpha-1 antitrypsin deficiency with the heterozygous Pi*MZ and homozygous Pi*ZZ genotype found in the community-based United Kingdom Biobank and the European Alpha1 liver consortium. While >80% of the individuals reported no/low alcohol intake, moderate alcohol intake resulted only in a minor increase in elevated transaminases in Pi*MZ individuals and non-carriers. In Pi*ZZ participants, moderate alcohol consumption had no impact on liver enzymes. Overall, our study provides robust data suggesting that moderate alcohol consumption is tolerated in the majority of individuals with alpha-1 antitrypsin deficiency.

Unhealthy alcohol consumption is responsible for at least 50% of the cases with liver cirrhosis.[11] Quantification of alcohol intake is usually carried out via self-reporting, although multiple biomarkers exist.[12] Carbohydrate-deficient transferrin (CDT) is the most widely used one due to its availability and good standardization.[13] While the threshold of moderate and harmful alcohol consumption is not unambiguously defined, long-term consumption of ≥5 drinks a day, corresponding to 60 g of alcohol, was associated with a 12 and 4 times increased risk of liver cirrhosis in females and

males, respectively.[14] Alcohol is even more damaging in subjects with chronic liver disease and/or disease cofactors, where no safe threshold exists.[15] For example, among subjects with moderate alcohol consumption, the presence vs. absence of metabolic syndrome yielded a ten-year risk for advanced liver disease of 1.4% and 0.3%, respectively.[16] As mentioned above, Pi*MZ status is an established co-factor for the development of alcoholic liver cirrhosis.[4] As a potential underlying mechanism, alcohol induces endoplasmic reticulum stress and promotes protein misfolding.[17] Notably, these factors are the primary drivers of AATD-associated liver disease.[4] These considerations and the real-life importance of this issue prompted us to systematically study the effect of alcohol consumption in Pi*MZ and Pi*ZZ subjects. Therefore, we combined the data available in the community-based United Kingdom Biobank (UKB) cohort with information/samples provided by the multinational European Alpha-1 Liver Study Group that focuses on the examination of subjects with severe AATD.

2 | METHODS

2.1 | Population-based UKB participants (cohort 1)

The multicenter, population-based UKB cohort consists of 502 511 individuals aged 37 to 73 years who were recruited from 2006 to 2010. All of them were registered with the UK National Health Service and were invited by post to come to one of the assessment centres. Informed consent for genotyping and data linkage to medical reports was given by all participants. The baseline assessment, that constitutes the focus of the current study, comprised of demographic and clinical data, laboratory analyses, and physical measures. Genotyping was performed either via the Affymetrix UK BiLEVE or the Affymetrix UK Biobank Axiom Array that both contain the Pi*Z (rs28929474) and Pi*S (rs17580) variants of *SERPINA1*. The latter as well as reported alcohol consumption was available in 487 503 subjects. UKB receives death reports (age at death and the corresponding ICD10 codes) through linkage to national death registries. The end of the follow-up was either death or the end of data collection in October 2022. Liver-related mortality was defined as liver transplantation after the baseline visit ($n = 50$), ICD-10 70–77, or C22 as the primary cause of death. Exclusion criteria comprised missing data on alcohol consumption, presence of Pi*S allele of *SERPINA1*, and viral hepatitis (B16-B19). The study has been approved by the UKB Access Committee (Project #71300).

2.2 | Adults of European Alpha1 liver consortium without previously known liver disease (cohort 2)

2.2.1 | Study population

From 1 April 2015 to 15 January 2022, 604 Pi*ZZ adults were recruited as part of the multicentric European Alpha1 liver consortium that offers prospective, longitudinal examinations to individuals of all AATD genotypes. The data used in this study comprised results from examinations of all Pi*ZZ individuals without previously known liver disease and with available blood sampling from eight European countries (Germany, United Kingdom, Spain, Denmark, Czech Republic, Sweden, Switzerland, and Austria). The cohort was in part described previously.[6,18] The evaluation of AAT genotype consisted of the measurement of AAT serum levels as well as genotyping via polymerase chain reaction and/or phenotyping via isoelectric focusing that were conducted by the corresponding national AAT reference laboratories.

Within the registry study, all participants underwent a detailed work-up for liver disease including standardized questionnaires with an evaluation of previous medical history, physical examination, laboratory analysis including the liver enzymes aspartate/alanine aminotransferase (AST/ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), serum-based liver fibrosis indices such as AST-to-platelet ratio index (APRI) and Fibrosis-4 index (Fib4), as well as a non-invasive assessment of liver fibrosis via transient elastography (TE) (FibroScan®, Echosens, Paris, France). Lung-related symptoms were evaluated via COPD assessment test (CAT) and modified British Medical Research Council Dyspnea Scale (mMRC). Lung-related parameters further included the total amount of cigarette consumption as well as a need for augmentation and long-term oxygen therapy (LTOT). The detailed individual mean daily alcohol consumption was assessed in a personal face-to-face interview with medical staff evaluating long-term drinking habits. Inclusion criteria for the study comprised (a) age ≥18 years, (b) no known pregnancy, (c) the ability to provide written informed consent, and (d) fasting for at least four hours prior to examination, whereas the following criteria led to exclusion: (a) non-European descent, (b) invalid liver stiffness measurement by TE or the presence of confounders of valid TE measurement, (c) the presence of known liver disease or a liver co-morbidity identified in clinical and laboratory examination.

2.2.2 | Recruitment of European Alpha1 liver consortium

The European Alpha1 liver consortium was built up through various campaigns and collaborations: (A) In 2015, the University Hospital Aachen became the coordinating centre for AATD-related liver disease within the framework of the European Reference Network (ERN) for rare hepatological diseases (ERN Rare Liver, www.rare-liver.eu) and was funded by a registry grant from the European Association of the Study of the Liver (EASL). (B) Awareness campaigns were carried out and included the establishment of an AATD liver-related website (www.alpha1-liver.eu), e-mail services, a telephone hotline for patients and physicians, as well as advertisements on social media. (C) Patients and physicians were informed via an intensive collaboration with patient advocacy groups, pulmonologists, German Gastroenterology Association, German Liver Foundation, and lung-centred AATD

registries. Liver examination days were performed in all participating European countries and a wide range of talks were held on patient meetings as well as scientific congresses. Furthermore, articles in patient-centred journals in various countries were used to increase awareness.

2.2.3 | Assessment of liver disease

The evaluation consisted of questionnaires, physical examination, and non-invasive liver stiffness measurement (LSM) for the assessment of the liver phenotype. Blood sampling was carried out. This included EDTA blood, which was drawn for genetic testing and was stored at +4°C as well as serum samples that were centrifuged, aliquoted, and stored at −80°C.

The measurement of liver fibrosis and liver steatosis via TE (FibroScan®, Echosens, Paris, France) was performed by experienced investigators who used the M or XL probe. Criteria for a valid assessment comprised at least 10 valid measurements with an interquartile range of ≤30% of the median LSM.[6] 20 Pi*ZZ individuals failed to meet these criteria and were excluded. The cut-offs for liver fibrosis were in line with aetiology-unspecific recommendations and previous publications: 7.1 kPa as an indicator for significant fibrosis (i.e., fibrosis stage ≥2) and 10 kPa for advanced liver fibrosis (i.e., fibrosis stage ≥3). Cut-offs for controlled attenuation parameter (CAP) as surrogate for liver steatosis were 248 dB/m for mild (i.e., steatosis grade ≥1) and 280 dB/m for severe steatosis (i.e., steatosis grade = 3).[6,18]

Liver comorbidity revealed by personal interview, laboratory analyses, as well as physical examination (e.g., liver transplant) led to exclusion. The comorbidities included the presence of autoimmune hepatitis (1 Pi*ZZ), chronic hepatitis B and C virus (7 Pi*ZZ), and hereditary hemochromatosis (3 Pi*ZZ individuals). Participants with histologically proven non-alcoholic steatohepatitis (NASH) were also excluded (6 Pi*ZZ subjects). The measurements of carbohydrate-deficient transferrin (CDT) were performed in the laboratory of Heidelberg University Hospital via high-performance liquid chromatography (HPLC). The analyses and quantitative detection of transferrin glycoproteins were carried out according to the published recommendation of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[19]

2.2.4 | Ethics

The study was registered with ClinicalTrials.gov (NCT02929940). Ethical approval was provided by the institutional review board of RWTH Aachen University (EK173/15) as well as the institutional ethics committees of participating centres. The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) as well as Good Clinical Practice (European guidelines).

2.3 | Statistical analysis

Categorical variables were shown as relative frequencies (%) and corresponding contingency tables were analysed via the chi-square test or Fisher's exact test as appropriate. Continuous variables were displayed as mean ± standard deviation (normal distribution) or median with interquartile range [IQR] (non-normal distribution) and analysed by unpaired, two-tailed t-tests or Mann–Whitney U test, respectively. A multivariable model was employed to account for relevant confounders (age, sex, BMI, and presence of diabetes mellitus). Multivariable logistic regression was performed to test for independent associations. Differences were considered to be statistically significant when $p < .05$. The data were analysed using SPSS Statistics version 28 (IBM; Armonk, NY, USA) and Prism version 9 (GraphPad, LaJolla, CA, USA).

3 | RESULTS

3.1 | Impact of moderate alcohol consumption on liver phenotype of UKB individuals (cohort 1)

We examined 487 503 participants of the United Kingdom Biobank (UKB) with available genotyping for AATD that included 425 002 individuals with Pi*MM, 17145 with Pi*MZ and 141 with Pi*ZZ genotype (Figure 1A). The subjects were divided based on their alcohol consumption into subgroups with no/low, moderate (women 12–39 g/d, men 24–59 g/d), and harmful alcohol consumption (women ≥40 g/d, men ≥60 g/d). In all examined genotypes, >80% of participants reported no/low alcohol intake, while harmful consumption was rare (<1% in Pi*MM/Pi*MZ, 2% in Pi*ZZ) (Supplemental Tables S1–S3). In Pi*MZ and Pi*MM subjects, individuals with moderate alcohol consumption showed lower BMIs than individuals with no/low consumption (Pi*MZ: 26.2 vs. 26.6 kg/m^2, $p < .001$; Pi*MM 26.4 vs. 26.8 kg/m^2, $p < .001$), whereas subjects with harmful consumption had the highest median BMI value (Pi*MZ 27.6 kg/m^2; Pi*MM 27.2 kg/m^2; Supplemental Tables S1 and S2). In both genotypes, the median age decreased with increasing alcohol consumption (Supplemental Tables S1 and S2). Sex distribution differed somewhat between the genotypes (Supplemental Tables S1–S3).

First, we compared liver enzymes among Pi*MM and Pi*MZ subjects with moderate vs. no/low consumption. As reported previously,[7] Pi*MZ individuals more often display elevated liver enzymes than Pi*MM subjects (Pi*MM, ALT 49.9 vs. 48.6% of ULN, $p < .001$; Pi*MZ ALT 52.2 vs. 51.1% of ULN, $p < .001$; Supplemental Tables S1 and S2). Notably, in both genotypes, moderate alcohol consumption resulted only in a minor increase in the rate of individuals with transaminases above the upper limit of normal (ULN) (Supplemental Tables S1 and S2; Figure 2A,B), while the effect on GGT was somewhat more pronounced (Pi*MM 23.0 vs. 15.0%, $p < .001$; Pi*MZ 22.5 vs. 15.7%, $p < .001$; Supplemental Tables S1

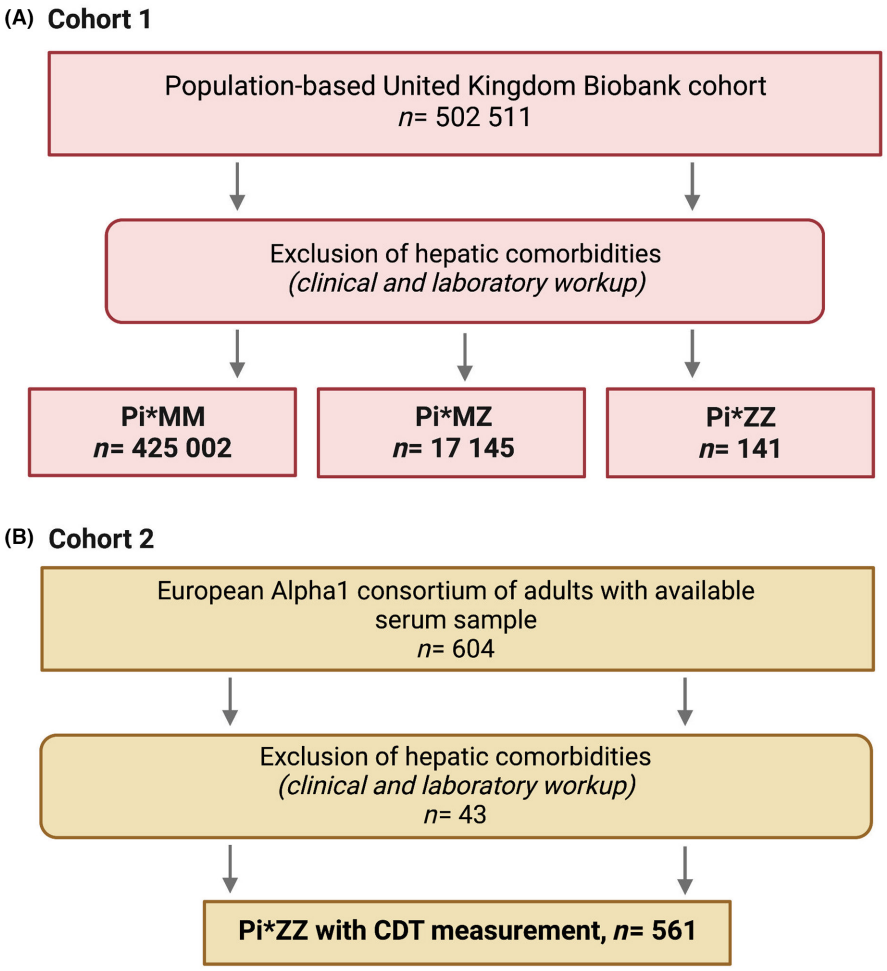

FIGURE 1 Overview of analysed cohorts. (A) Cohort 1: Population-based cohort of United Kingdom Biobank (UKB) with participants aged 37–73 years at baseline. (B) Cohort 2: Cross-sectional cohort of Pi*ZZ adults from the European Alpha1 liver consortium with available serum sample. CDT, carbohydrate-deficient transferrin.

and S2; Figure 2C). Other examined liver surrogates (i.e., bilirubin, platelets) did not indicate a stronger liver injury in subgroups with moderate vs. no/low alcohol consumption, ALP values were even lower (Supplemental Tables S1 and S2). In contrast to that, APRI as a surrogate of liver fibrosis tended to be slightly higher in subjects with moderate vs. no/low alcohol intake. This was particularly true for the fraction of subjects with APRI ≥1.00 suggestive of advanced fibrosis that was higher in individuals with moderate vs. no/low alcohol intake and the difference was seen in both genotypes (Pi*MM .9 vs. .6%, $p < .001$; Pi*MZ 1.2 vs. .6%, $p = .002$; Supplemental Tables S1 and S2; Figure 2D). However, the overall rates were very low (.6%–1.2%). Anamnestic alcohol consumption did not have a significant effect on the median fibrosis-4 index (Supplemental Tables S1 and S2). Among Pi*MM subjects, those with moderate vs. no/low alcohol consumption had twofold higher rate of liver-related death (.4 vs. .2, $p < .001$), while the overall mortality was lower in the former group (6.2 vs. 8.2, $p < .001$, Supplemental Tables S1 and S2). No significant differences in overall and liver-related death were seen among Pi*MZ participants (Supplemental Tables S1 and S2). Collectively, these data indicate that moderate consumption is well tolerated in the majority of subjects of both genotypes. While the number of Pi*ZZ individuals was too low to reach definitive conclusion, subjects with moderate alcohol intake did not display a significant increase in any of the examined surrogates of liver injury (Supplemental Table S3).

3.2 | Impact of harmful alcohol consumption in UKB Biobank (cohort 1)

Next, we focused on the consequences of harmful alcohol consumption. In both Pi*MM and Pi*MZ, it resulted in a marked increase in the proportion of individuals with elevated transaminases (Supplemental Tables S1 and S2; Figure 2A,B) as well as elevated GGT (Supplemental Tables S1 and S2; Figure 2C). Notably, the effect was similar in both genotypes. Other examined liver surrogates (i.e., bilirubin, ALP, platelets) did not indicate a stronger liver injury in subgroups with harmful vs. no/low alcohol consumption, ALP values were even lower (Supplemental Tables S1 and S2). In contrast, APRI as a surrogate of liver fibrosis was again higher in subjects with harmful vs. no/low alcohol intake in both genotypes (Supplemental Tables S1 and S2; Figure 2D). The occurrence of liver-related death and overall mortality was higher in subjects with harmful consumption compared to no/low and moderate intake, but it failed to reach statistical significance in Pi*MZ subjects (Supplemental Tables S1

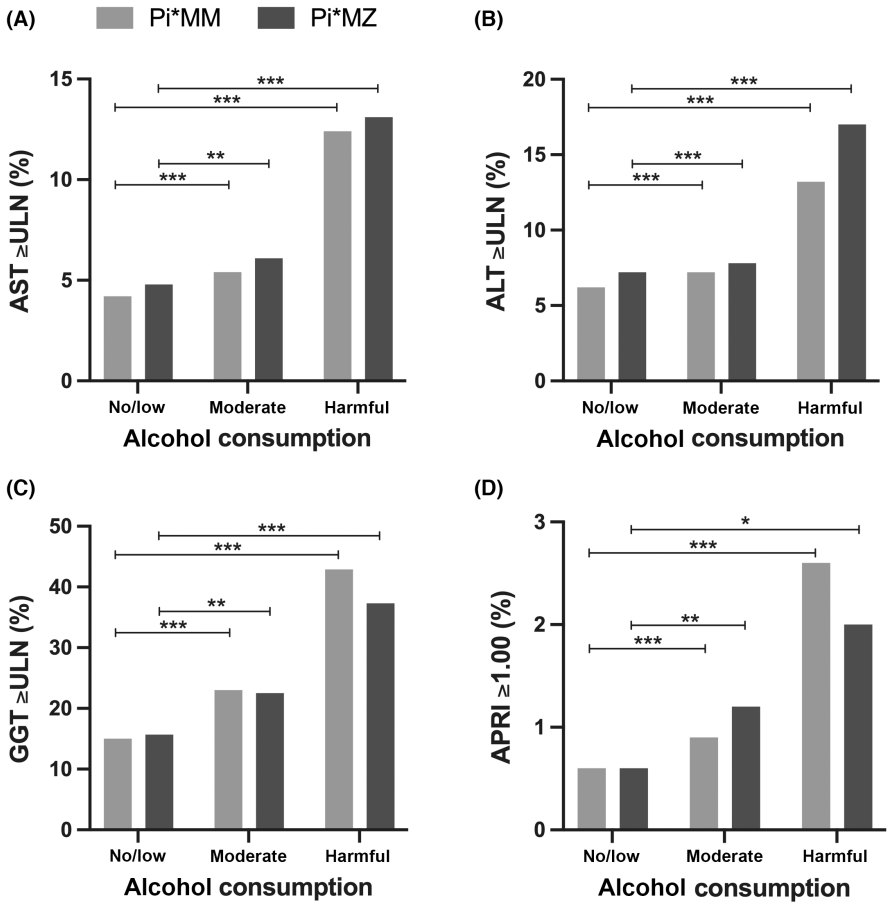

FIGURE 2 Liver enzymes and liver-related death in Pi*MM and Pi*MZ individuals from the United Kingdom Biobank depending on anamnestic alcohol consumption (cohort 1). Proportion of Pi*MM individuals and Pi*MZ subjects with (A) AST, (B) ALT, or (C) GGT above the upper limit of normal, as well as (D) APRI≥1.00 in relation to the reported alcohol consumption: "no/low alcohol consumption": Women 0–11 g/d, men 0–23 g/d; "moderate alcohol consumption": Women 12–39 g/d, men 24–59 g/d; "harmful alcohol consumption": Women≥40 g/d, men≥60 g/d. *$p < .05$, **$p < .01$, ***$p < .001$. ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, sex-specific upper limit of normal.

and S2). Collectively, these data suggest that harmful consumption promotes liver injury to a similar extent in both genotypes. Due to low numbers, no meaningful conclusions could be drawn in Pi*ZZ subjects (Supplemental Table S3).

3.3 | Reported alcohol consumption and liver phenotype of Pi*ZZ individuals from the European Alpha1 liver consortium (cohort 2)

In the European Alpha1 liver consortium, we examined 561 Pi*ZZ adults without hepatic comorbidities and available serum samples (Figure 1B). 129 of them (23%) displayed LSM ≥7.1 kPa suggestive of fibrosis stage ≥2 (Table 1). 91% and 8% of participants reported no/low and moderate alcohol consumption, respectively (Table 1). Age/sex distribution, AAT serum levels, and lung-related parameters were comparable (Supplemental Table S4). The differences in liver enzymes did not reach statistical significance. While subjects with harmful alcohol intake displayed the highest levels of most liver enzymes, the numbers were too low to reach statistical significance (Supplemental Table S4, Figure 3A–C). Non-invasive markers of liver fibrosis and liver steatosis did not display relevant differences between subgroups (Supplemental Table S4; Figure 3D–F). Overall, these data indicate that lower alcohol consumption is well tolerated in Pi*ZZ subjects while further studies are needed to evaluate the consequences of harmful alcohol intake.

3.4 | Association between CDT values and liver phenotype of Pi*ZZ individuals from the European Alpha1 liver consortium (cohort 2)

86% of Pi*ZZ participants displayed normal (i.e., <1.7%) CDT values and these reported significantly lower alcohol consumption than subjects with elevated CDT levels (Supplemental Table S5). In univariable but not multivariable analysis, Pi*ZZ individuals with elevated CDT levels displayed higher GGT serum levels as well as higher APRI scores (Supplemental Table S5 and Figure S1). There were no significant differences in liver fibrosis or liver steatosis parameters evaluated by TE (Supplemental Figure S1).

3.5 | Combined alcohol assessment and liver phenotype of Pi*ZZ individuals from the European Alpha1 liver consortium (cohort 2)

Finally, we combined both parameters and divided the Pi*ZZ participants with elevated CDT values into subgroups with no/low (60

TABLE 1 Characteristics of Pi*ZZ individuals from the European Alpha1 liver consortium (cohort 2).

	Male $n=296$	Female $n=265$	Total $n=561$		
Characteristics					
Age (years)	55.9 [47.1–62.6]	57.1 [49.5–65.1]	56.3 [48.5–63.7]		
BMI (kg/m^2)	25.1 [23.0–28.1]	23.8 [21.1–26.6]	24.6 [22.0–27.5]		
Mean alcohol consumption (g/d)	2.5 [.0–8.2]	1.3 [.0–5.3]	1.6 [.0–6.5]		
AAT serum level (mg/dL)[a]	23.5 [20.4–30.1]	24.2 [20.8–29.5]	24.1 [20.5–29.9]		
Modifiable risk factors					
BMI ≥30 kg/m^2 (%)	16.4	12.2	14.4		
Diabetes mellitus (%)	3.7	3.8	3.7		
Moderate alcohol intake[b] (%)	8.1	9.8	8.9		
AAT augmentation (%)	51.7	44.9	48.5		
mMRC	0	1	2	3	4
Male/female (%)	56/53 (18.9/20.0)	90/76 (30.4/28.7)	48/51 (16.2/19.2)	33/35 (11.1/13.2)	9/11 (3.0/4.2)
LSM (kPa)	<7.1	7.1–10	10.1–14.9	≥15	
Male/female (%)	185/218 (62.5/82.3)	44/25 (14.9/9.4)	30/5 (10.1/1.9)	20/5 (6.8/1.9)	
CAP (dB/m)	<248	248–279	≥280		
Male/female (%)	84/114 (28.4/43.0)	57/51 (19.3/19.2)	114/72 (38.5/27.2)		

Note: Quantitative measures are expressed as median with interquartile range or as relative frequency (%).

Abbreviations: AAT, alpha-1 antitrypsin; BMI, body mass index; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; mMRC, modified British Medical Research Council Dyspnea Scale.

[a]AAT serum levels of individuals who did not receive AAT augmentation therapy are shown.

[b]Alcohol intake >12 g/d women, >24 g/d men.

subjects) and at least moderate reported alcohol consumption (19 subjects) (Tables 2 and 3). The groups were termed CDT consumers (i.e., subjects with at least moderate reported alcohol consumption and CDT ≥1.7%) and CDT non-consumers (i.e., subjects with no/low reported alcohol consumption, but CDT ≥1.7%) (Table 2). The control group of non-drinkers was defined by normal CDT values and no/low reported alcohol consumption. CDT non-consumers were significantly more often males than non-drinkers (Table 2). CDT serum levels were comparable in CDT consumers and non-consumers (Table 2). CDT non-consumers presented with higher GGT serum levels (72.5 vs. 60.0, $p=.020$, Table 3) and higher APRI (.36 vs. .30, $p=.008$, Table 3) compared to non-drinkers, they also had a higher proportion of subjects with APRI ≥1.00 (8.9 vs. 3.2%, $p=.038$, Table 3) indicative of advanced liver fibrosis. Overall, these data indicate that assessment of CDT levels might be useful in subjects with signs of significant liver disease but no/minimal reported alcohol intake and may indicate an unreported alcoholism. However, the numbers are low and the numbers in both groups differ substantially. Therefore, validation studies are needed.

4 | DISCUSSION

In the present study, we examined the association between alcohol consumption and liver phenotype in two large AATD cohorts. An advantage of the UKB cohort is the fact that AATD subjects are detected via systematic genetic screening which is important since the majority of Pi*MZ subjects remain undetected their whole life.[2] Therefore, UKB represents the currently best approximation of a population-based AATD cohort. Since it contains only a limited number of Pi*ZZ subjects, we assessed the multinational cohort from the European Alpha1 liver consortium as the world-wide largest Pi*ZZ cohort with available liver phenotyping.[6]

The major finding of our study is that moderate alcohol consumption seems to be relatively well tolerated in the majority of Pi*MZ and Pi*ZZ subjects. This is in line with a previous report that did not find an association between alcohol consumption and the presence of advanced liver disease in Pi*ZZ subjects,[20] but in contrast with manuscripts describing higher rates of liver cirrhosis in Pi*MZ subjects with alcohol misuse.[7,9] Therefore, AATD subjects might be susceptible to higher alcohol doses while being relatively insensitive to lower amounts.[9] Given the proteotoxic nature of the disease, the impact of alcohol on protein degradation might be particularly important. With regard to that acute alcohol exposure as well as exposure to lower levels may induce autophagy while chronic ingestion of high alcohol amounts blocks it. The proteasomal protein degradation also becomes inhibited primarily after a prolonged, extensive alcohol intake.[21] In line with this hypothesis, Mallory-Denk bodies, the protein inclusions characteristic of alcoholic liver disease (ALD), are particularly numerous in most severe ALD cases while they are rare in simple alcoholic steatosis. Other factors of known importance in AATD that are triggered by higher rather than low

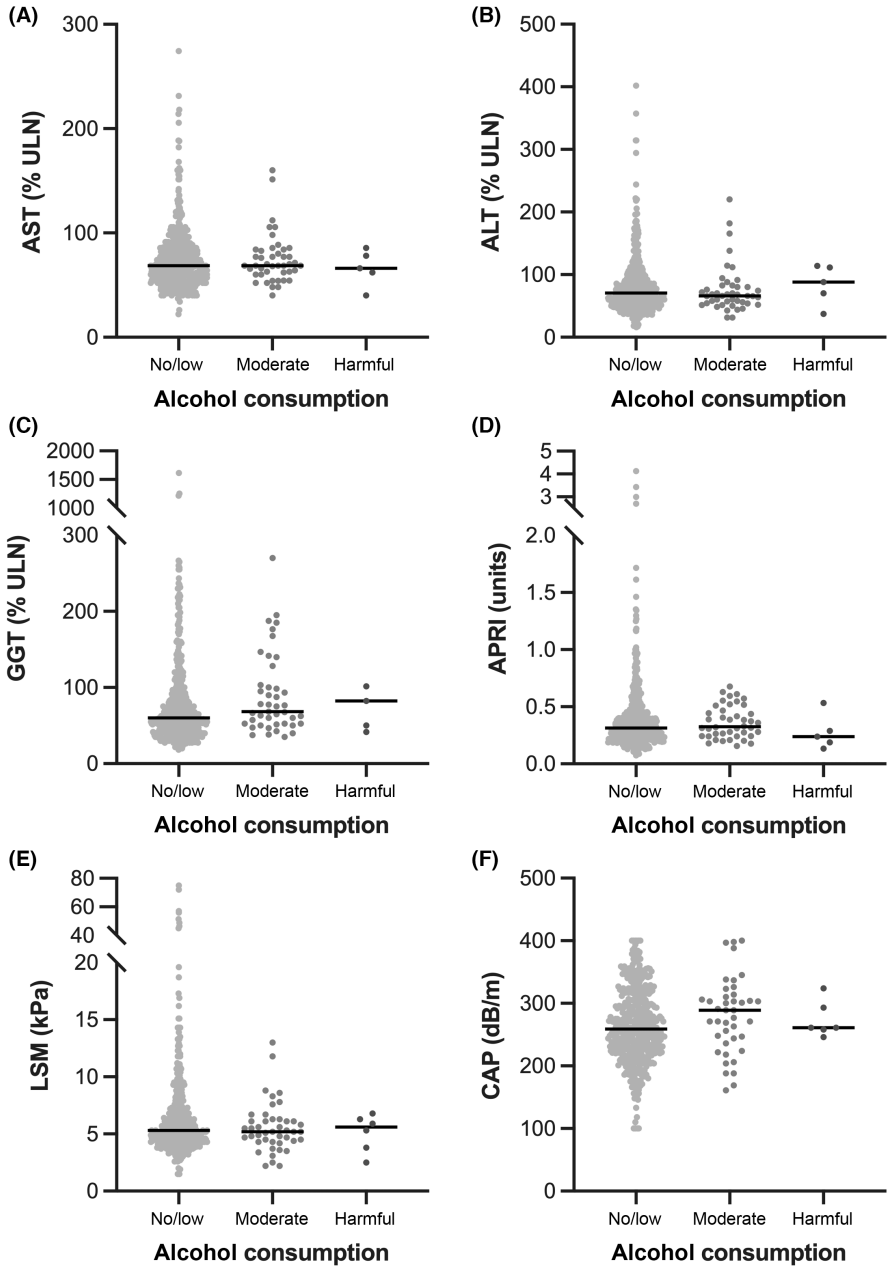

FIGURE 3 Liver-related parameters in Pi*ZZ participants from the European Alpha1 liver consortium (cohort 2) in relation to reported alcohol consumption. (A, B) Scatter plots of AST, ALT, as well as (C) gamma-glutamyl transferase (GGT) values and (D) APRI indices in 511 Pi*ZZ individuals with no/low alcohol consumption (women 0–11 g/d, men 0–23 g/d), 44 PI*ZZ participants with moderate alcohol consumption (women 12–39 g/d, men 24–59 g/d), and 6 Pi*ZZ subjects with harmful alcohol consumption (women ≥40 g/d, men≥60 g/d). Values in (A–C) were normalized and are shown as the percentage of ULN. (E) Liver stiffness measurements (LSM) and (F) controlled attenuation parameters (CAP) assessed via vibration-controlled transient elastography (VCTE) as indicators of liver fibrosis and steatosis, respectively. ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; LSM, liver stiffness measurement; ULN, sex-specific upper limit of normal.

alcohol consumption include endoplasmic reticulum stress and cytokine-driven acute phase response that induces AAT synthesis.[1]

While our data suggest a modest impact of moderate alcohol intake in both examined cohorts, these findings do not exclude a damaging effect even of low alcohol consumption in selected individuals. Regarding the latter, Pi*MZ subjects with moderate alcohol consumption had twice as higher occurrence of APRI ≥1.00, indicating the presence of advanced liver fibrosis. Another factor contributing to the complexity of this issue is the fact that subjects with advanced liver fibrosis often underestimate their actual alcohol consumption.[22] In line with that, CDT non-consumers presented with significantly higher GGT serum levels and APRI compared to non-drinkers (Table 3). Therefore, we encourage a regular assessment of alcohol biomarkers in AATD individuals with advanced liver fibrosis, particularly those considered for liver transplantation. While more data are needed to evaluate the influence of harmful alcohol consumption in Pi*ZZ subjects, the findings from UKB (i.e., significantly higher occurrence of APRI ≥1.00) clearly suggest that such consumption should be discouraged in this fragile patient population that displays a 20 times elevated risk of liver cirrhosis.[4,8] Moreover, individuals with advanced liver fibrosis should abstain from any alcohol consumption.[23]

Our study has several important limitations. It relies to a large extent on publicly available data that were only in part validated in an additional, original cohort. It is based primarily on anamnestic alcohol consumption that may not always be accurate. While the latter has been somewhat mitigated by the assessment of CDT values in the European Pi*ZZ cohort, these measurements are not available in UK Biobank. The fact that 80% of the individuals included in the cohorts belong to the "no/low alcohol intake" category decreased

TABLE 2 Characteristics of Pi*ZZ participants from the European Alpha1 liver consortium in relation to reported alcohol consumption and CDT values (cohort 2).

	Group 1: non-drinkers (*CDT and anamnesis negative*) $n = 451$	Group 2: CDT consumers (*CDT and anamnesis positive*) $n = 19$	Group 3: CDT non-consumers (*CDT positive, anamnesis negative*) $n = 60$	*p* value 1 versus 2 (*univariable*)	*p* value 1 versus 3 (*univariable*)
Characteristics					
Age (years)	56.4 [48.4–64.7]	57.5 [53.5–62.8]	56.6 [49.2–61.3]	.441	.392
Women (%)	50.1	31.6	21.7	.113	**<.001**
BMI (kg/m^2)	24.5 [21.6–27.5]	26.3 [23.5–28.3]	24.5 [22.4–29.8]	.212	.161
Mean alcohol consumption (g/d)	.6 [.0–5.0]	27.4 [25.1–38.4]	2.9 [.0–9.8]	**<.001**	**.007**
AAT serum level (mg/dL)[a]	23.5 [20.5–29.4]	29.2 [29.2–29.2]	25.6 [20.7–36.7]	.523	.229
Modifiable risk factors					
BMI ≥30 kg/m^2 (%)	14.1	15.8	22.4	.741	.094
Diabetes mellitus (%)	3.3	.0	8.3	.419	.060
CDT (%)	.95 [.69–1.18]	2.17 [1.80–3.07]	2.15 [1.87–3.14]	**<.001**	**<.001**
Moderate alcohol intake (%)[b]	.0	100.0	.0	**<.001**	
Lung status					
CAT (points)	16.0 [9.0–22.0]	15.0 [12.0–23.0]	16.0 [9.5–22.0]	.388	.751
mMRC (grade)	1.0 [.0–2.0]	1.0 [1.0–2.0]	1.0 [1.0–2.0]	.785	.287
Pack years	15.0 [7.5–25.0]	15.0 [10.0–25.0]	13.0 [6.5–31.0]	.931	.655
LTOT (%)	14.0	21.1	23.3	.331	.057
AAT augmentation (%)	46.8	68.4	51.7	.064	.477

Note: Grouping was based on CDT and anamnestic alcohol consumption (g/d). Group 1: CDT <1.7% and no/low anamnestic alcohol consumption (women <12 g/d, men <24 g/d); Group 2: CDT ≥1.7% and moderate anamnestic alcohol consumption (women ≥12 g/d, men ≥24 g/d); Group 3: CDT ≥1.7% and no/low anamnestic alcohol consumption (women <12 g/d, men <24 g/d). Significant *p*-values are highlighted in bold.

Abbreviations: AAT, alpha-1 antitrypsin; BMI, body mass index; CAT, COPD assessment test; CDT, carbohydrate-deficient transferrin; LTOT, long-term oxygen therapy; mMRC, modified British Medical Research Council Dyspnea Scale.

[a]AAT serum levels of individuals who did not receive AAT augmentation therapy are shown.

[b]Alcohol intake >12 g/d women, >24 g/d men.

TABLE 3 Liver status of Pi*ZZ individuals from the European Alpha1 liver consortium in relation to reported alcohol consumption and CDT values (cohort 2).

	Group 1: non-drinkers (*CDT and anamnesis negative*) *n* = 451	Group 2: CDT consumers (*CDT and anamnesis positive*) *n* = 19	Group 3: CDT non-consumers (*CDT positive, anamnesis negative*) *n* = 60	*p* value 1 versus 2 (*univariable*)	*p* value 1 versus 3 (*univariable*)
Liver-related blood parameters					
ALT (% of ULN)	70.0 [51.4–92.0]	68.0 [56.0–88.0]	75.1 [56.0–101.0]	.849	.168
ALT ≥ULN (%)	20.7	15.8	27.6	.776	.229
AST (% of ULN)	68.6 [54.3–85.7]	66.0 [60.0–84.0]	68.6 [59.5–90.4]	.929	.260
AST ≥ULN (%)	12.2	21.1	17.2	.280	.282
GLDH (% of ULN)	48.6 [30.0–74.3]	57.4 [44.1–117.4]	47.9 [36.0–87.5]	.124	.323
GLDH ≥ULN (%)	13.4	31.3	20.5	**.045**	.204
GGT (% of ULN)	60.0 [41.7–91.7]	70.8 [51.3–102.1]	72.5 [50.8–111.3]	.130	**.020**
GGT ≥ULN (%)	22.5	33.3	27.6	.286	.392
ALP (% of ULN)	62.9 [51.4–77.7]	59.1 [42.1–67.9]	57.7 [47.7–67.9]	.166	.062
ALP ≥ULN (%)	8.3	5.6	6.9	.678	.714
Bilirubin (% of ULN)	.53 [.38–.71]	.57 [.43–.82]	.58 [.46–.80]	.384	.065
Bilirubin ≥ULN (%)	5.5	5.6	10.5	.991	.134
Platelets (G/L)	235.5 [190.0–279.0]	223.0 [179.0–281.0]	222.5 [173.5–265.0]	.692	.160
Platelets <150 G/L (%)	10.3	15.8	8.9	.438	.752
INR (units)	1.01 [.96–1.07]	1.00 [.93–1.03]	1.03 [.96–1.08]	.121	.553
Liver status					
Fib4	1.27 [.86–1.79]	1.57 [1.01–1.92]	1.33 [1.01–1.80]	.224	.281
Fib4 ≥1.3 (%)	48.5	63.2	51.8	.212	.646
APRI	.30 [.22–.43]	.33 [.24–.53]	.36 [.27–.55]	.319	**.008**
APRI ≥50 (%)	18.5	31.6	28.6	.157	.076
APRI ≥1.00 (%)	3.2	.0	8.9	.428	**.038**
Liver stiffness (kPa)	5.3 [4.4–7.0]	5.6 [4.2–6.8]	5.8 [4.5–8.7]	.542	.195
LSM ≥7.1 kPa (%)	24.4	21.1	32.1	.738	.211
LSM ≥10.0 kPa (%)	11.5	.0	16.1	.249	.323
CAP (dB/m)	258.0 [224.0–301.0]	294.5 [246.8–308.0]	268.0 [227.0–332.3]	.064	.197
CAP ≥248 dB/m (%)	58.3	72.2	59.6	.239	.853
CAP ≥280 dB/m (%)	35.6	55.6	44.2	.086	.226

Note: Grouping was based on CDT and anamnestic alcohol consumption (g/d). Group 1: CDT <1.7% and no/low anamnestic alcohol consumption (women <12 g/d, men <24 g/d); Group 2: CDT ≥1.7% and moderate anamnestic alcohol consumption (women ≥12 g/d, men ≥24 g/d); Group 3: CDT ≥1.7% and no/low anamnestic alcohol consumption (women <12 g/d, men <24 g/d). "≥ULN (%)" refers to the percentage of individuals with values above the ULN. Significant *p*-values are highlighted in bold.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CDT, carbohydrate-deficient transferrin; Fib4, fibrosis-4 index; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; INR, international normalized ratio; LSM, liver stiffness measurement; ULN, sex-specific upper limit of normal.

our ability to evaluate the effect of higher alcohol intake. Because of that, despite the fact that Pi*MZ individuals with harmful alcohol intake had surprisingly low GGT/APRI levels, an harmful alcohol consumption should be clearly discouraged in all subjects and in particular in Pi*MZ/Pi*ZZ individuals given that the negative effect of alcohol misuse on Pi*MZs has been demonstrated in several well-performed studies.[7,9] Finally, multiple additional biomarkers of alcohol consumption exist and should be evaluated in future studies. Among them, phosphatidylethanol quantification in blood seems to be more reliable and accurate than CDT.[24] Moreover, the impact of alcohol in other AATD genotypes remains to be examined and the same is true for interaction with additional modifiers such as obesity or diabetes. Notably, the European Alpha1 cohort had a proportion of MASLD subjects comparable or even lower than usual in

the Western world. Finally, APRI is an imperfect surrogate of liver fibrosis given that its component AST is affected by alcohol consumption, but LSM values are not available in the UK Biobank cohort. The above-suggested analyses should allow a more in-depth insight into the impact of alcohol on AATD subjects and are therefore warranted.

Notwithstanding the above-described limitations of our work and the fact that the harm of even low alcohol intake that has been demonstrated in large, well-performed prospective studies,[25] our observation will be helpful for the management and counselling of AATD patients. In particular, repeatedly elevated liver enzymes (particularly transaminases) should not be disregarded as an expected consequence of moderate alcohol consumption, but rather lead to a thorough clinical work-up, given that they are uncommon even in Pi*ZZ subjects and are associated with higher liver fibrosis stages.[5–7] Subjects without significant liver fibrosis and normal liver enzymes who constitute the majority of Pi*ZZ subjects do not seem to be at higher liver-related risk than Pi*MM individuals when moderately consuming alcohol. Nevertheless, they should be offered a regular check-up given their highly increased risk of liver fibrosis. On the other hand, biomarkers of alcohol consumption, such as CDT, should be assessed in individuals with advanced liver disease as well as in candidates for the ongoing clinical trials to unambiguously clarify the potential contribution of this key co-factor.[26]

To sum up, the AATD Pi*MZ/Pi*ZZ genotype does not seem to significantly aggravate the hepatic toxicity of moderate alcohol consumption. CDT values might be helpful to detect alcohol consumption in those with advanced fibrosis.

AUTHOR CONTRIBUTIONS

Study concept and design: M.F., P.S. Acquisition of data: M.F., C.V.S, N.G., S.A., Y.L., M.P., J.G., M.M., K.T., M.M., J.W., K.M.S., J.S., S.F., M.B., H.Z., M.Z., A.K., A.T., C.T., P.S. Analysis and interpretation of data: M.F., C.V.S., N.G., P.S. Drafting of the manuscript: M.F., P.S., C.T. Critical revision of the manuscript for important intellectual content: all authors. Figures and tables: M.F., C.V.S., N.G., P.S. Statistical analysis: M.F., C.V.S., N.G. Obtained funding: M.F., P.S., N.G., C. T. Study supervision: M.F., P.S. All authors approved the final version of this manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

M.F. received consulting fees from Takeda Pharmaceuticals and honoraria from CSL Behring, Grifols and Takeda Pharmaceuticals. P.S. received grant support and lecture fees from Grifols and CSL Behring, grant support and advisory board fees from Arrowhead Pharmaceuticals and Dicerna Pharmaceuticals, grant support from Vertex Pharmaceuticals, advisory board fees from GSK, Intellia Pharmaceuticals, NovoNordisk, Takeda and Ono Pharmaceuticals. M.M. has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols and Novartis, consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, ONO Pharma, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi, Zambon and Grifols and research grants from Grifols. AT received grant support from CSL Behring, Grifols Biotherapeutics and Vertex Pharmaceuticals, honoraria from Boehringer Ingelheim, GSK, AstraZeneca, Takeda. All authors declare themselves independent of funders concerning this manuscript.

DATA AVAILABILITY STATEMENT

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

FURTHER REMARKS

We attest that we did not use any copyright-protected material in our manuscript. No writing assistance was provided.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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