Real-World Burden of Nonalcoholic Steatohepatitis

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BACKGROUND & AIMS: **Nonalcoholic steatohepatitis (NASH) is associated with an increase in healthcare resource use and poor health-related quality of life (HRQoL). We assessed the humanistic and economic burden of NASH, disease management, and patient journey.**

METHODS: **We performed a cross-sectional analysis of data, collected from July through November 2017, from the Growth from Knowledge Disease Atlas Real-World Evidence program, reported by physicians in United States, France, and Germany. We extracted demographic and medical data from medical records. Some patients voluntarily completed a survey that provided information on disease history, treatment satisfaction, and patient-reported outcomes.**

RESULTS: **We analyzed data from 1216 patients (mean age, 54.9±12.3 years; 57.5% male; mean body mass index, 31.7±6.9); 64.6% had biopsy-confirmed NASH and comorbidities were recorded for 41.3%. Treatments included lifestyle modification (64.6%) or use of statins (25.0%), vitamin E (23.5%), or metformin (20.2%). Patients with biopsy-confirmed NASH reported more physician (4.5 vs 3.7) and outpatient visits (1.8 vs1.4) than patients with suspected NASH not confirmed by biopsy. Among the 299 patients who completed the survey, 47.8% reported various symptoms associated to their NASH. Symptomatic patients reported significantly lower HRQoL than patients without symptoms.**

CONCLUSIONS: **In an analysis of data from 3 countries, we found NASH to be associated with regular use of medical resources; patients with symptoms of NASH had reduced HRQoL. The burden of NASH appears to be underestimated. Studies are needed to determine the burden of NASH by fibrosis stage and disease severity.**

Keywords: Fatty Liver; PROS; Medical Resources; Treatment.

Nonalcoholic steatohepatitis (NASH) is the most severe form of nonalcoholic fatty liver disease involving excessive liver fat accumulation, inflammation, fibrosis, and hepatocyte ballooning, which can lead to cirrhosis.[1] Progression to cirrhosis can take up to 20 years but can be faster (7–10 years) in certain patients.[2,3]

Suspicion of NASH is based on a series of noninvasive tests (phenotypic NASH), and diagnosis confirmed by liver biopsy (biopsy-confirmed NASH).[4] However, liver biopsy is not routinely performed.[4] Currently, NASH is the second leading cause of liver transplantation in adults in the United States,[5,6] indicating the long-term burden of NASH if left untreated. In the absence of approved pharmacologic treatment options, the current standard of care involves lifestyle modification (diet, exercise, weight loss) and comorbidity management.[4]

Nonalcoholic fatty liver disease (including NASH) is associated with increased health care resource use[7] and a poor health-related quality of life (HRQoL).[8-10] Additional research is warranted to characterize the overall burden of NASH. The objective of this study was to assess the HRQoL and economic burden of NASH and to

Abbreviations used in this paper: **CLDQ, Chronic Liver Disease Questionnaire; HRQoL, health-related quality of life; NASH, nonalcoholic steatohepatitis; SD, standard deviation; WPAI-SHP, Work Productivity and Activity Impairment – Specific Health Problem.**

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characterize patient profiles, including disease management and the patient journey.

What You Need to Know

Background

Nonalcoholic steatohepatitis (NASH) is associated with an increase in healthcare resource use and poor health-related quality of life.

Findings

In an analysis of data from 3 countries, NASH was associated with regular use of medical resources and reduced health-related quality of life.

Implications for patient care

The burden of NASH might be underestimated. More studies are needed to determine how NASH affects patients' lives, and the changes that occur with increasing disease severity.

Methods

Study Design, Sampling, and Data Source

This was a noninterventional, cross-sectional analysis of data collected between July and November 2017, by the Growth from Knowledge (currently Ipsos) Disease Atlas Real-World Evidence program (NASH-Atlas) among physicians in the United States, France, and Germany. The study uses a published methodology applied in other disease areas.[11]

Study participants. Participating physicians included gastroenterologists, hepatologists, and internists with a special interest in hepatology with 3–30 years' experience, involved in the management and treatment of patients with NASH.

Physicians recruited the next 5–10 consecutive eligible patients following regular consultation and based on study-defined inclusion and exclusion criteria. Inclusion criteria were (1) known diagnosis of NASH either by liver biopsy or a combination of clinical, laboratory, and imaging parameters with physician clinical judgement (phenotypic NASH); (2) eligible for liver biopsy but not performed; (3) under the care of the physician for at least 6 months; and (4) willing to complete a pen and paper survey without physician intervention after their consultation. Exclusion criteria was presence of any other liver condition.

Study questionnaires. Physicians completed study-specific patient record forms developed by the study team. Data collected included demographics; disease characteristics; diagnostic tests; treatment history; and health care resource use, such as nonroutine NASH-related specialist physician visits (with the physicians participating in the study), outpatient visits (with other physicians), inpatient admissions, emergency room visits, and the number of nights in hospital and/or intensive care unit. Physicians were asked to extract these data from the patient medical charts for the period since they started managing the patients.

The patients' survey was developed by the study team and contained study-specific questions (demographics, history of disease, symptoms leading to their initial doctor consultation, current symptoms, and satisfaction with current management), and 3 validated patient-reported outcome measures. The Chronic Liver Disease Questionnaire (CLDQ) measures HRQoL across 6 domains (abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry) over a 2-week recall period.[12] Total and domain scores range from 1 (most impairment) to 7 (least impairment). The EQ-5D-5L is a standardized, generic patient-reported outcome measure consisting of a descriptive part with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a 20-cm Visual Analogue Scale. For each dimension, patients respond on a 5-level scale ranging from no problems to extreme problems on the day of assessment. A single utility score is calculated ranging from 0 (death) to 1 (full health). The Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) assesses absenteeism, presenteeism, overall work impairment (for employed respondents), and overall activity impairment (for all respondents) caused by NASH in the past 7 days. Scores are reported as percentages on a scale of 0%–100%; higher scores indicate greater impairment.

Statistical Analysis

Descriptive and bivariate analyses were conducted on the pooled cohort and specific subgroups, and by country. Categorical variables are presented as number and percentage of patients in each category. Continuous variables are reported as mean and standard deviation (SD). The analysis of each outcome reported was performed on observed data only (ie, missing values were excluded from all analyses).

Secondary analyses were performed by 2 subgroups: biopsy-confirmed versus phenotypic NASH and by symptom status (symptomatic vs asymptomatic). Chi-square tests were used for all categorical dependent variables, and 1-way analysis of variance was used for continuous variables. Associations between 2 continuous variables were assessed using a 2-tailed Pearson correlation coefficient; all findings with $P < .05$ were considered statistically significant.

Each annual health care resource listed previously (eg, outpatient visits, in-hospital stay, intensive care unit visits) was estimated by calculating the mean monthly use per patient while under the physician's care, and then multiplying it by 12 months. It was reported using means and SD for the pooled cohort and by subgroups of interest.

Table 1. Patient Demographics and Medical Records Data, Pooled and by Country

Patient demographics	Pooled (N = 1216)	United States (N = 702)	France (N = 227)	Germany (N = 287)
Age, *y* (mean, SD)	54.9 (12.3)	53.5 (12.6)	56.9 (12.9)	56.9 (10.3)
Male, n (%)	699 (57.5)	384 (54.7)	147 (64.8)	168 (58.5)
Female, n (%)	517 (42.5)	318 (45.3)	80 (35.2)	119 (41.5)
Ethnicity[a], n (%)	n = 989[a]	n = 702	—	n = 287
White	633 (64.0)	407 (58.0)	—	226 (78.7)
Hispanic/Latino	147 (14.9)	126 (17.9)	—	21 (7.3)
Black African/Black Caribbean/African American	100 (10.1)	94 (13.4)	—	6 (2.1)
Others	88 (8.9)	54 (7.7)	—	34 (11.8)
Unknown	21 (2.1)	21 (3.0)	—	0 (0.0)
BMI				
BMI (mean, SD)	31.7 (6.9)	32.7 (7.4)	31.7 (5.9)	29.1 (5.7)
BMI category, n (%)				
Underweight (<18.5)	3 (0.2)	0 (0.0)	1 (0.4)	2 (0.7)
Normal/healthy weight (18.5–24.9)	140 (11.5)	76 (10.8)	16 (7.0)	48 (16.7)
Overweight (25.0–29.9)	397 (32.6)	196 (27.9)	70 (30.8)	131 (45.6)
Obese (30.0–34.9)	382 (31.4)	213 (30.3)	89 (39.2)	80 (27.9)
Morbidly obese (>35.0)	294 (24.2)	217 (30.9)	51 (22.5)	26 (9.1)
NASH diagnosis, n (%)				
Biopsy-confirmed	786 (64.6)	497 (70.8)	104 (45.8)	185 (64.5)
Phenotypic	430 (35.4)	205 (29.2)	123 (54.2)	102 (35.5)
Fibrosis stage at NASH diagnosis (biopsy-confirmed cohort), n (%)	n = 786	n = 497	n = 104	n = 185
No fibrosis	55 (7.0)	44 (8.9)	1 (1.0)	10 (5.4)
Fibrosis stage 1 (F1)	175 (22.3)	123 (24.7)	11 (10.6)	41 (22.2)
Fibrosis stage 2 (F2)	278 (35.4)	154 (31.0)	49 (47.1)	75 (40.5)
Fibrosis stage 3 (F3)	211 (26.8)	127 (25.6)	29 (27.9)	55 (29.7)
Fibrosis stage 4 (F4)	47 (6.0)	30 (6.0)	13 (12.5)	4 (2.2)
Unknown stage of fibrosis	20 (2.5)	19 (3.8)	1 (1.0)	0 (0.0)

BMI, body mass index; NASH, nonalcoholic steatohepatitis; SD, standard deviation.
[a]Ethnicity data could not be collected for patients from France.

Results

Pooled Data

Patient demographics and clinical patient profile. Medical record forms of 1216 patients were included in the analysis; 64.6% of these patients had biopsy-confirmed NASH. The mean ± SD age was 54.9 ± 12.3 years, body mass index was 31.7 ± 6.9, 57.5% were male, and 64.0% were White. More than half of the patients were obese or morbidly obese (Table 1, Supplementary Table 1).

Comorbidity was recorded for 502 (41.3%) patients, most common being type 2 diabetes mellitus, hypertension, and obesity (Figure 1). The patients were managed by the participating physicians since 26.72 ± 1.07 months.

First diagnosis of NASH was made by a gastroenterologist for 46.7% patients, hepatologist for 24.2%, primary care physician/general practitioner for 9.8%, and the remaining were diagnosed by other health care professionals. On first presentation to the treating physician, 69.5% of patients had no symptoms, 17.4% had fatigue, 13.7% had abdominal bloating/swelling, 12.7% had abdominal pain/discomfort, and 11.7% of patients experienced malaise. Weight gain was recorded for 10.6% of patients, sleep apnea/disturbance (7.1%), pruritus (5.3%), and jaundice (4.8%).

At the time of data collection, 58.0% of patients were symptomatic and had experienced symptoms for 27.0 ± 24.5 months.

Diagnosis, monitoring, and disease management. The mean ± SD time between the NASH diagnosis and inclusion in the study was 31.0 ± 40.2 months. Liver biopsy was performed at least once in 66.0% of patients for diagnostic purposes and in 11.6% of patients for monitoring purposes. The most used noninvasive tests and procedures for diagnosis of NASH were ultrasound, FibroScan, lipid profile, platelet count, serum transaminase, and γ-glutamyltransferase levels (Figure 2*A*). Serum transaminases and ultrasound were the most common tests used for disease monitoring (Supplementary Table 2, Supplementary Figure 1).

At the time of diagnosis (phenotypic or biopsy-confirmed), the immediate next course of action taken by the physician was to recommend lifestyle modification in 55.9% of patients, perform additional evaluations in 36.1%, and perform a liver biopsy in 33.1%.

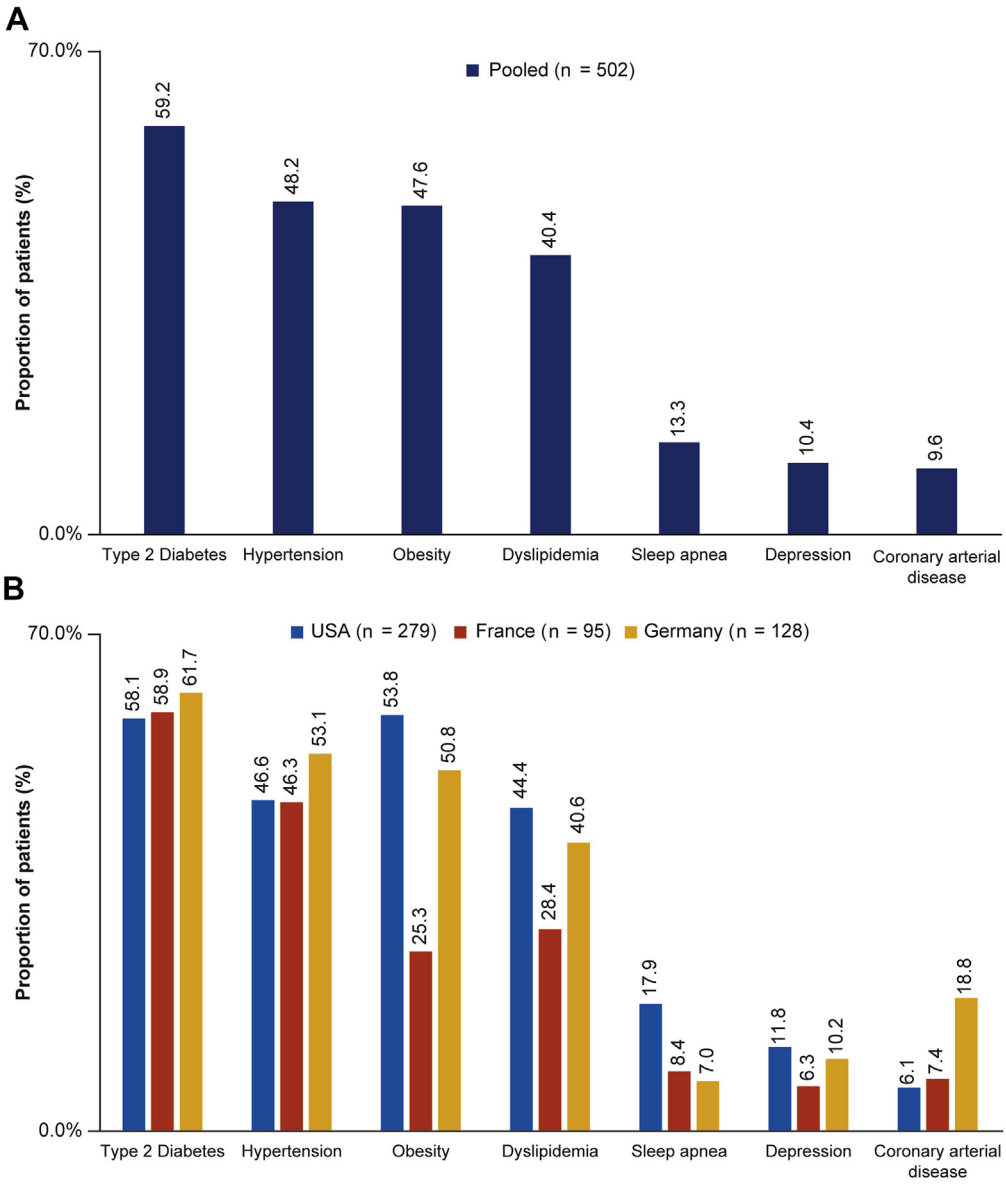

Figure 1. Frequency of comorbidities (percentage in the subgroup of patients with recorded available data [n = 502]) recorded in the medical records. (*A*) Pooled cohort. (*B*) Across countries.

The mean ± SD duration from NASH diagnosis to initiation of the first treatment (nonpharmacologic or pharmacologic) was 24.4 ± 29.2 months. Among all patients who were ever prescribed a pharmacologic treatment, the mean ± SD time from NASH diagnosis to first prescription was 13.1 ± 20.7 months overall; this ranged from 13.9 ± 22.1 months for biopsy-confirmed NASH patients to 11.2 ± 17.5 months for phenotypic NASH patients. Similar treatment approaches were reported regardless of how NASH was diagnosed; lifestyle modification was the leading recommendation in both groups. At the time of the study, lifestyle modification was recommended in 64.6% of patients, followed by statins (25.0%), vitamin E (23.8%), and metformin (20.2%) (Supplementary Figure 2). The most common reason for initiating pharmacologic treatment and/or closely monitoring a patient's NASH was elevated liver enzymes (50.3%).

Health care resource use. The mean ± SD annual nonroutine NASH-related physician visits was 4.2 ± 3.1, outpatient visits 1.6 ± 2.0, and inpatient visits 0.3 ± 0.9. Moreover, patients with NASH in this study had a mean ± SD of 0.3 ± 1.0 emergency room visits, 3.7 ± 7.1 nights in the hospital, and 0.4 ± 1.2 nights in the intensive care unit because of NASH calculated over a period of a year. The mean number of nonroutine NASH-related physician visits and inpatient visits were higher for biopsy-confirmed NASH patients compared with phenotypic NASH patients, except for NASH-related nights in the hospital (Figure 3).

Descriptive Comparative Results by Country

Among the study cohort, 702 (57.7%) patients were from the United States, 227 (18.7%) from France, and 287 (23.6%) from Germany. Patients from the United States were slightly younger than patients from Europe. The proportion of male patients was higher than female

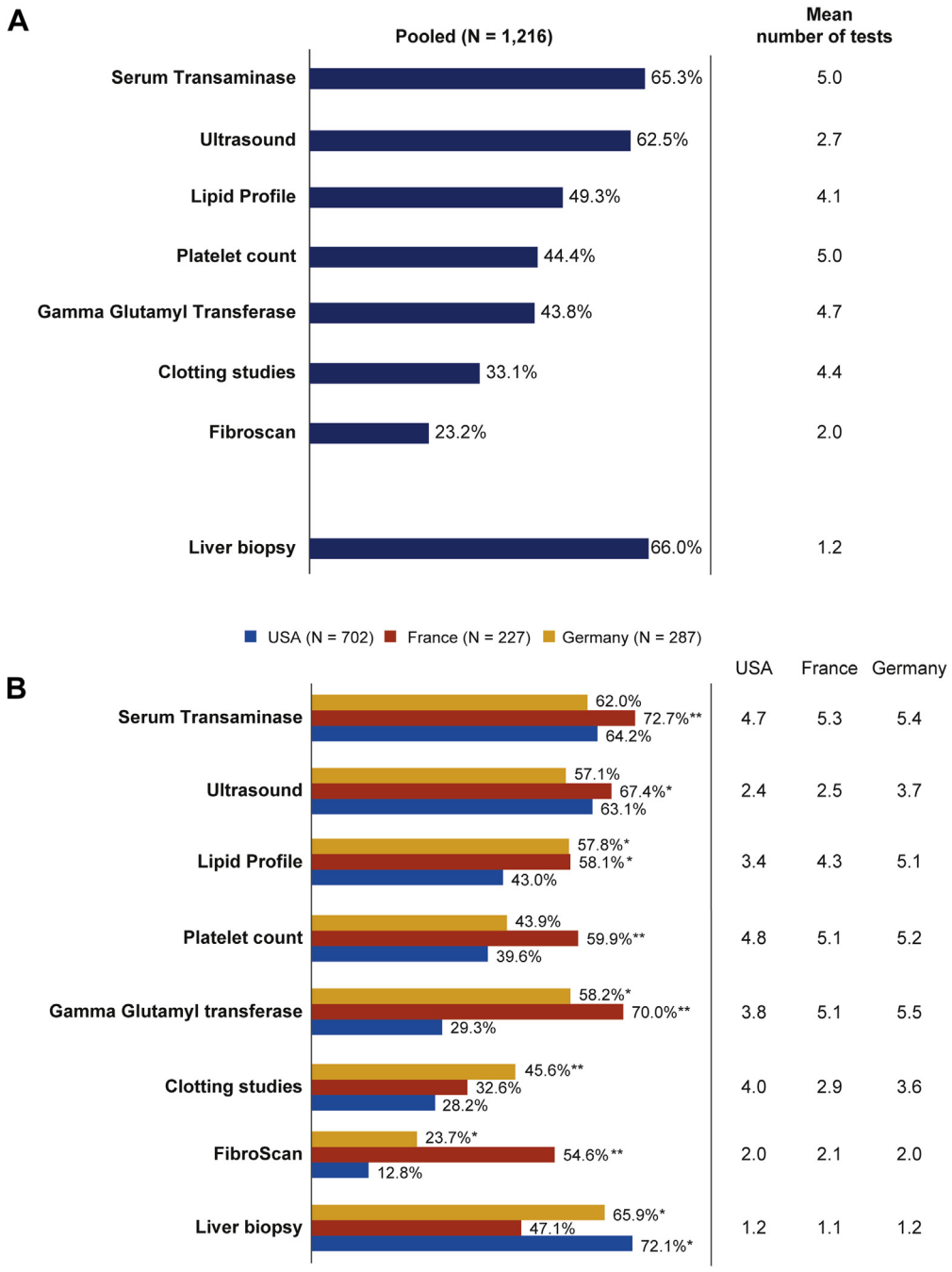

Figure 2. Tests and procedures conducted at least once as part of diagnosis and mean number of tests per patient (diagnosis and monitoring) while under physician management. (*A*) Pooled cohort. (*B*) Across countries. *Significant difference compared with the lowest reporting country ($P < .05$). **Significant difference compared with all other countries.

in each country (Table 1). Among symptomatic patients, the most common symptom was fatigue in patients from the United States (51.9%) and France (64.6%) and malaise in patients from Germany (66.7%). The proportion of patients reporting other symptoms, such as pruritus and sleep apnea, was similar across countries. The mean time between symptom onset and inclusion in this study was the longest in France (35.0 months) compared with the United States (26.3 months) and Germany (21.7 months). Liver biopsy was performed in 72.1% of patients in the United States, 47.1% of patients in France, and 65.9% of patients in Germany. Common noninvasive tests performed to aid NASH diagnosis were similar across countries with serum transaminase, platelet count, and γ-glutamyltransferase being the most commonly performed tests (Figure 2*B*, Supplementary Table 3).

At the time of the study, lifestyle modification was recommended for 70.5% of patients in the United States, 61.2% of patients in France, and 53.0% of patients in Germany. Among patients who were prescribed a pharmacologic treatment as their initial NASH treatment, the most common was vitamin E (29.6%) in the United States, statins (22.6%) in Germany, and ursodeoxycholic acid (21.6%) in France. Elevated liver enzyme levels were the most common reason for initiating pharmacologic treatment and/or closely monitoring patients' NASH. No significant difference was noted in the annual

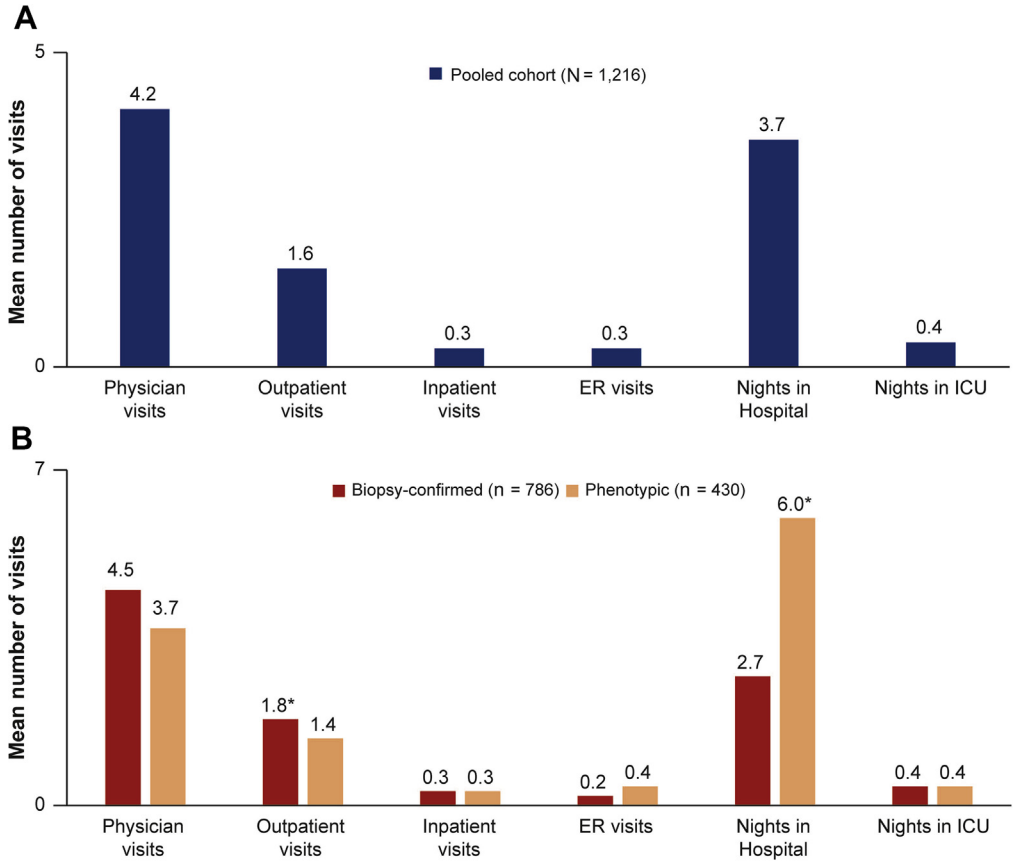

Figure 3. Annual nonroutine health care resource use in (*A*) pooled cohort and (*B*) biopsy-confirmed and phenotypic NASH patients. Physician visits refers to nonroutine NASH physician visits (with the participating physicians). Outpatient visits refers to visits with other physicians. *Statistically significant difference ($P < .05$). ER, emergency room; ICU, intensive care unit.

health care resource use across countries (Supplementary Figure 3).

Impact of Nonalcoholic Steatohepatitis From the Patient-Reported Outcomes

A total of 299 patients completed the patient survey. Of these, 160 had biopsy-confirmed NASH (Table 2). The mean ± SD age was 54.9 ± 13.7 years, 61.9% of patients were male, and 47.8% reported symptoms attributed to fatty liver disease before the diagnosis of NASH. Fatigue was the main symptom that influenced patients to seek medical consultation (Table 2).

Initial suspicion of a liver condition was incidental in 34.4% of patients following a routine general practitioner check-up. When asked to rate their perception of the severity of their fatty liver disease when first diagnosed, 54.2% of patients reported it to be moderate to severe. At the time of the study, 68.9% of patients reported experiencing various symptoms, with fatigue being the most common and most bothersome symptom (Table 2).

Health-related quality of life. The mean ± SD CLDQ score in the pooled cohort was 5.10 ± 1.43 (Supplementary Table 4). The level of impairment among symptomatic patients was significantly higher compared with asymptomatic patients in the pooled and biopsy-confirmed cohorts (Figure 4*A* and *B*). Across all CLDQ domains, the symptomatic patients (pooled or biopsy-confirmed) reported significantly lower scores compared with the asymptomatic ones, indicating greater impairment in liver-related QoL.

The mean ± SD EQ-5D-5L utility score in the pooled cohort was 0.83 ± 0.21 (Supplementary Table 4). The most impacted dimensions were pain/discomfort, usual activities, and anxiety/depression, for which more patients reported moderate to extreme problems. Symptomatic patients reported lower mean ± SD utility scores compared with asymptomatic patients in the pooled (0.77 ± 0.2 vs 0.94 ± 0.15) and biopsy-confirmed (0.78 ± 0.17 vs 0.98 ± 0.05) cohorts, indicating a significantly poorer HRQoL. Similarly, a higher proportion of symptomatic patients reported problems across all dimensions compared with asymptomatic patients (Supplementary Figure 4).

Impact on work (Work Productivity and Activity Impairment – Specific Health Problem). In the subgroup of employed patients (Table 2) who completed the WPAI-SHP questionnaire, the mean ± SD percentage impairment in terms of absenteeism, presenteeism, and overall work impairment was 9.0% ± 22.5%, 17.5% ± 19.9%, and 24.7% ± 27.4%, respectively; the mean ± SD activity impairment in the entire cohort was 30.7% ± 28.5% (Supplementary Table 4). The mean scores for all WPAI

Table 2. Patient Profile Among Pooled and Biopsy-Confirmed NASH Cohort Completing the Patient Survey

Patient demographics	Pooled (n = 299)	Biopsy-confirmed NASH (n = 160)
Age, *y* (mean, SD)	54.9 (13.7)	54.2 (12.0)
Male, n (%)	185 (61.9)	99 (61.9)
Female, n (%)	114 (38.1)	61 (38.1)
Working status, n (%)		
Employed	141 (47.2)	79 (49.4)
Unemployed	36 (12.0)	17 (10.6)
Retired	82 (27.4)	39 (24.4)
Other	40 (13.4)	25 (15.6)
Signs and symptoms before diagnosis influencing first doctor visit		
Number experiencing symptoms, n (%)[a]	143 (47.8)	82 (51.3)
Fatigue	87 (60.8)	47 (57.3)
Malaise	56 (39.2)	29 (35.4)
Abdominal bloating	54 (37.8)	32 (39.0)
Decreased strength	48 (33.6)	21 (25.6)
Weight gain	47 (32.9)	31 (37.8)
Abdominal pain	43 (30.1)	27 (32.9)
Sleep apnea	22 (15.4)	14 (17.1)
Pruritus	16 (11.2)	10 (12.2)
Mental problems	15 (10.5)	7 (8.5)
Swelling in legs/ankles/feet	15 (10.5)	9 (11.0)
Jaundice	10 (7.0)	9 (11.0)
Others	19 (13.3)	8 (9.8)
Signs and symptom status at the time of study, n (%)		
No symptoms	93 (31.1)	48 (30.0)
Number experiencing symptoms[a]	206 (68.9)	112 (70.0)
Fatigue	115 (55.8)	60 (53.6)
Malaise	73 (35.4)	40 (35.7)
Abdominal bloating and swelling	78 (37.9)	41 (36.6)
Weight gain	43 (20.9)	31 (27.7)
Abdominal pain	45 (21.8)	21 (18.8)
Sleep apnea	32 (15.5)	18 (16.1)
Pruritus	20 (9.7)	10 (8.9)
Jaundice	15 (7.3)	8 (7.1)
Others	20 (9.7)	8 (3.9)

NASH, nonalcoholic steatohepatitis; SD, standard deviation.
[a]Patients could report multiple signs and symptoms.

dimensions were higher for symptomatic patients versus asymptomatic patients indicating greater impairment (Figure 4*C* and *D*).

Discussion

This observational study assessed the burden of disease in real-world settings describing patient profiles, strategies used for the diagnosis and management of NASH, and medical resource use associated with NASH. It also describes symptoms associated with NASH and the impact of NASH on patients' HRQOL and work.

NASH is often reported as a silent asymptomatic disease but recent evidence suggests that many patients have multiple symptoms that are not always directly attributed to NASH.[13] The study confirms that a high proportion of patients experience various symptoms, such as fatigue, abdominal bloating and pain, pruritus, and sleep problems. Fatigue was the most common symptom influencing a patient to seek medical consultation. Pruritus is a new finding in our study lately reported in other recent studies.[14-16] The initial suspicion of a liver condition was often incidental following a routine general practitioner check-up and later confirmed by specialists including gastroenterologists or hepatologists.

In other published studies it is reported that up to 70% of patients with NASH had comorbidities,[17,18] but in our study, comorbidities were reported in 41% of patients, with type 2 diabetes mellitus and hypertension being the most common. One discrepancy noted in our data was that only 239 patients had a clinical diagnosis of obesity, whereas a body mass index $\geq$30 (obese/morbidly obese) was recorded in 676 patients.

Our results report that a liver biopsy was performed in 66.0% of patients for diagnosis purposes and 11% of patients had a second biopsy to monitor the disease progression. Noninvasive tests, such as liver enzyme and

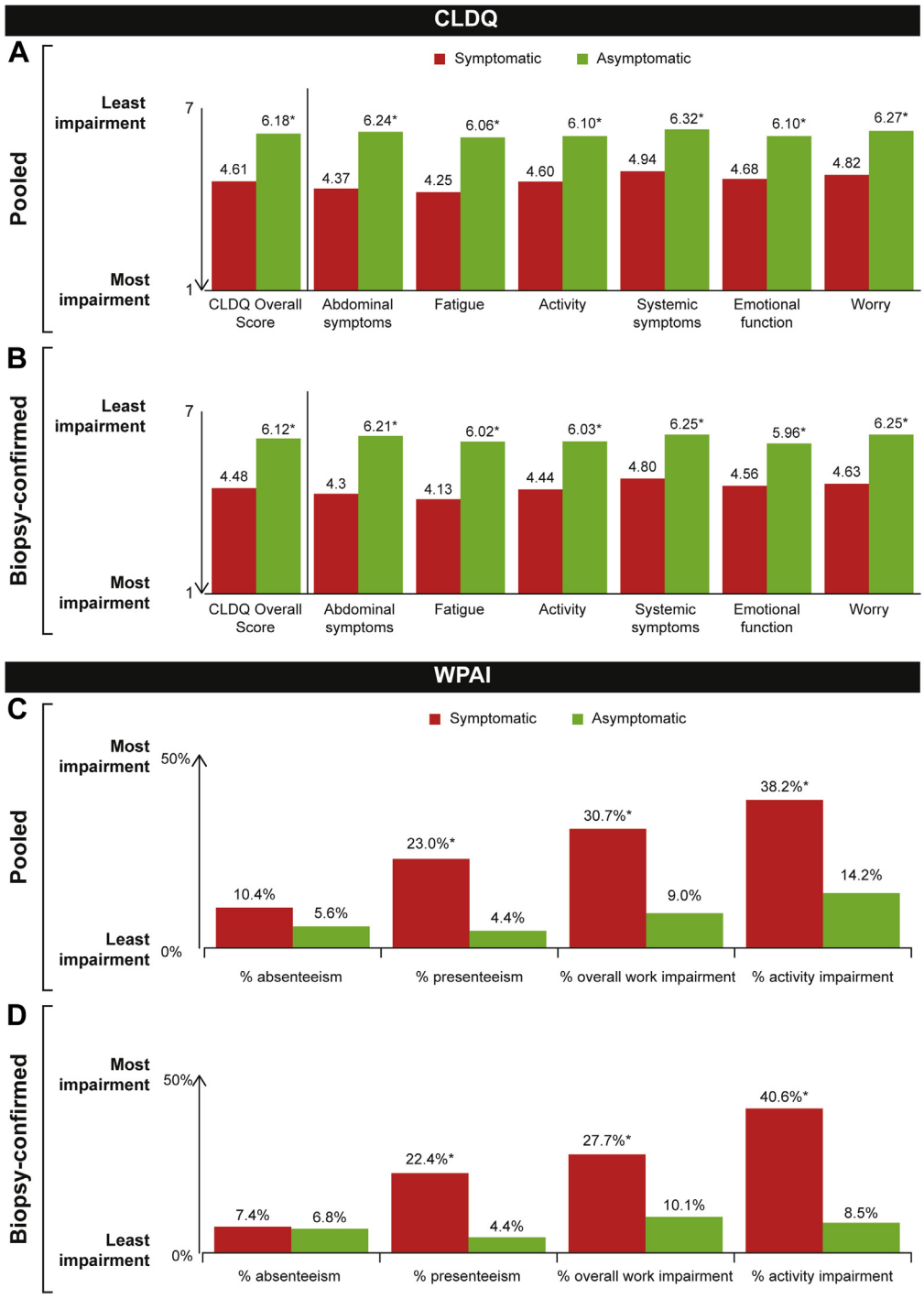

Figure 4. Results of CLDQ in pooled cohort (*A*) and biopsy-confirmed (*B*) and WPAI in pooled cohort (*C*) and biopsy-confirmed (*D*). *Significant difference between comparative groups ($P < .05$).

lipid profile, together with ultrasound were used frequently to monitor patients. To date, there are no approved specific treatments for NASH.[19,20] This might explain why lifestyle modification was the leading recommendation followed by the prescription of treatments to treat comorbidities.

Many studies have reported on the economic burden of nonalcoholic fatty liver disease, but with limited description of the actual resource use or the burden of NASH.[7] This study describes the resource use associated with NASH, which comprises outpatient/inpatient visits, nights in hospital, and emergency room visits. These findings reveal that NASH is associated with a higher medical resource use than generally perceived.

NASH negatively impacts the patients' HRQoL, daily life, and capacity to work.[10] This study provides comprehensive evidence on the burden of NASH based on generic and liver-specific patient-reported outcome measures and reveals the domains mostly affected by the condition. Symptomatic patients showed significantly worse overall and liver-related QoL and a higher work

impairment compared with asymptomatic patients. The CLDQ scores reported by the patients in this study are comparable with the ones reported across other chronic liver diseases[12,21,22] and the impact on work and daily activities (WPAI scores) is consistent with that in other published studies.[23]

The comparative country data showed consistent findings, but it also showed some differences among the countries, which might be explained by differences in health care systems, accessibility of procedures, local management practices, and guidelines.

These data should be interpreted in the context of features of a real-world cross-sectional study.

Our study has several limitations. The lack of longitudinal data might limit the full description of treatment patterns and resource use over time. The study included patients with a NASH diagnosis and the decision was based on the clinical judgment and diagnostic skills of the participating physician because not all patients had a liver biopsy–confirmed NASH. Not all patients eligible for the study agreed to participate, and only a small proportion agreed to complete the patient survey. Furthermore, because of the cross-sectional nature of the study there was no site monitoring or quality control to ensure that the physicians obtained all the data from the medical charts.

Conclusions

This study reveals the current profile and journey of patients with NASH and quantifies the HRQoL and economic burden. Patients with NASH report low HRQoL and high use of medical resources. Despite the burden imposed by NASH, lifestyle modification was the most common recommendation, thereby confirming the need for targeted therapies to treat liver injury and research on the long-term outcomes. Finally, this research reflects the status of diagnosis and management of patients with NASH at the time of study execution. As the field evolves changes in clinical practice and availability of future treatments might influence findings if a similar study was repeated.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.06.064.

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Conflicts of interest
These authors disclose the following: Andreas Geier, Mary Rinella, and Vlad Ratziu received a consultancy fee for their medical expertise on this project from Novartis Pharma AG, Basel. Maria-Magdalena Balp is an employee of Novartis Pharma AG, Basel, Switzerland. Clifford Brass, Raymond Przybysz, and Jennifer Cai are employees of Novartis Pharmaceuticals Corporation. Amanda Knight, Meghan Gavaghan, Tanya Howe, and Daniel Rosen were employees of GfK Health at the time of the study, which Ipsos has since acquired. Tanya Howe and Meghan Gavaghan are current employees of Ipsos. Sarah Jane McKenna is an employee of Novartis Business Services Centre, Ireland.

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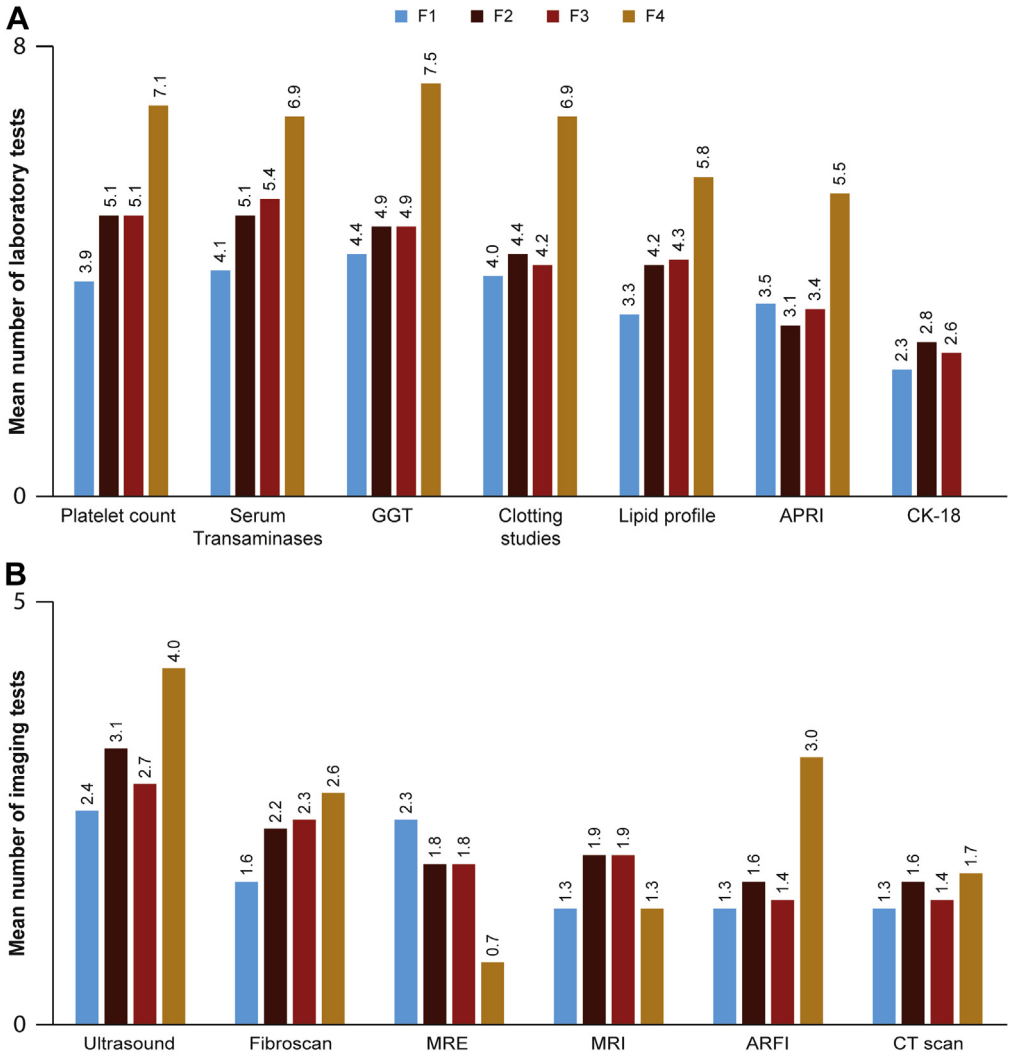
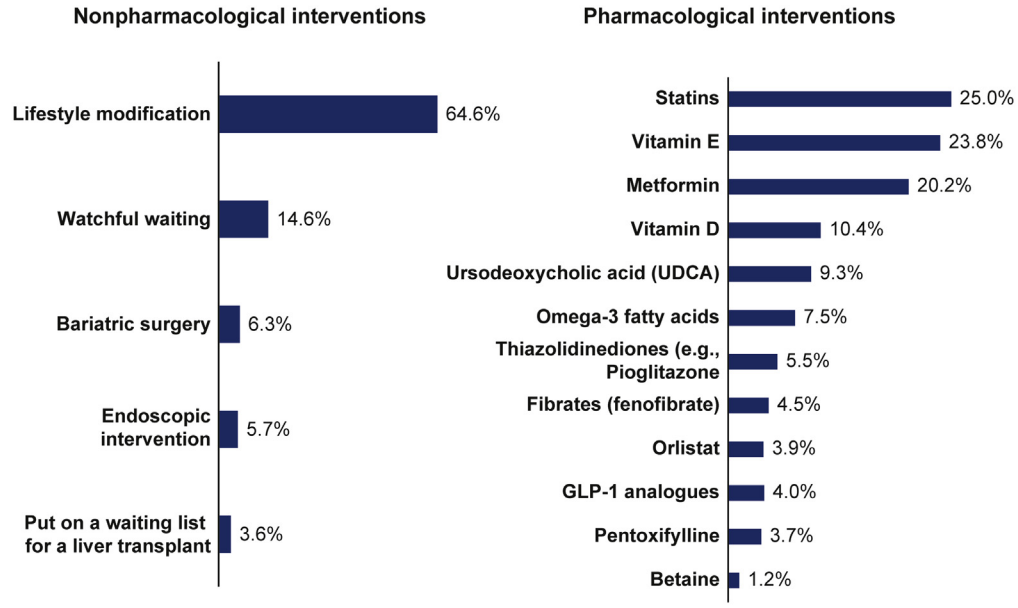
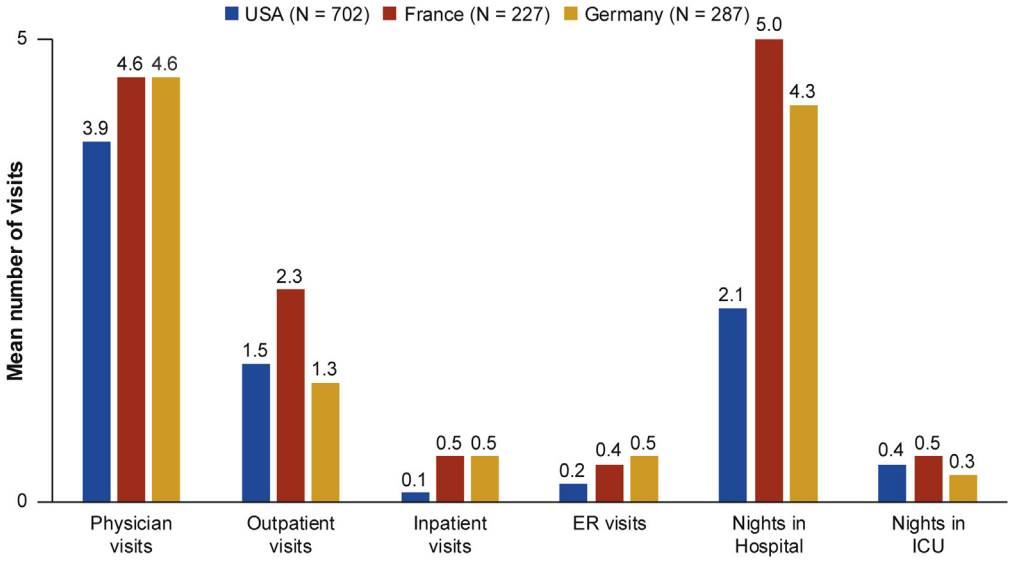


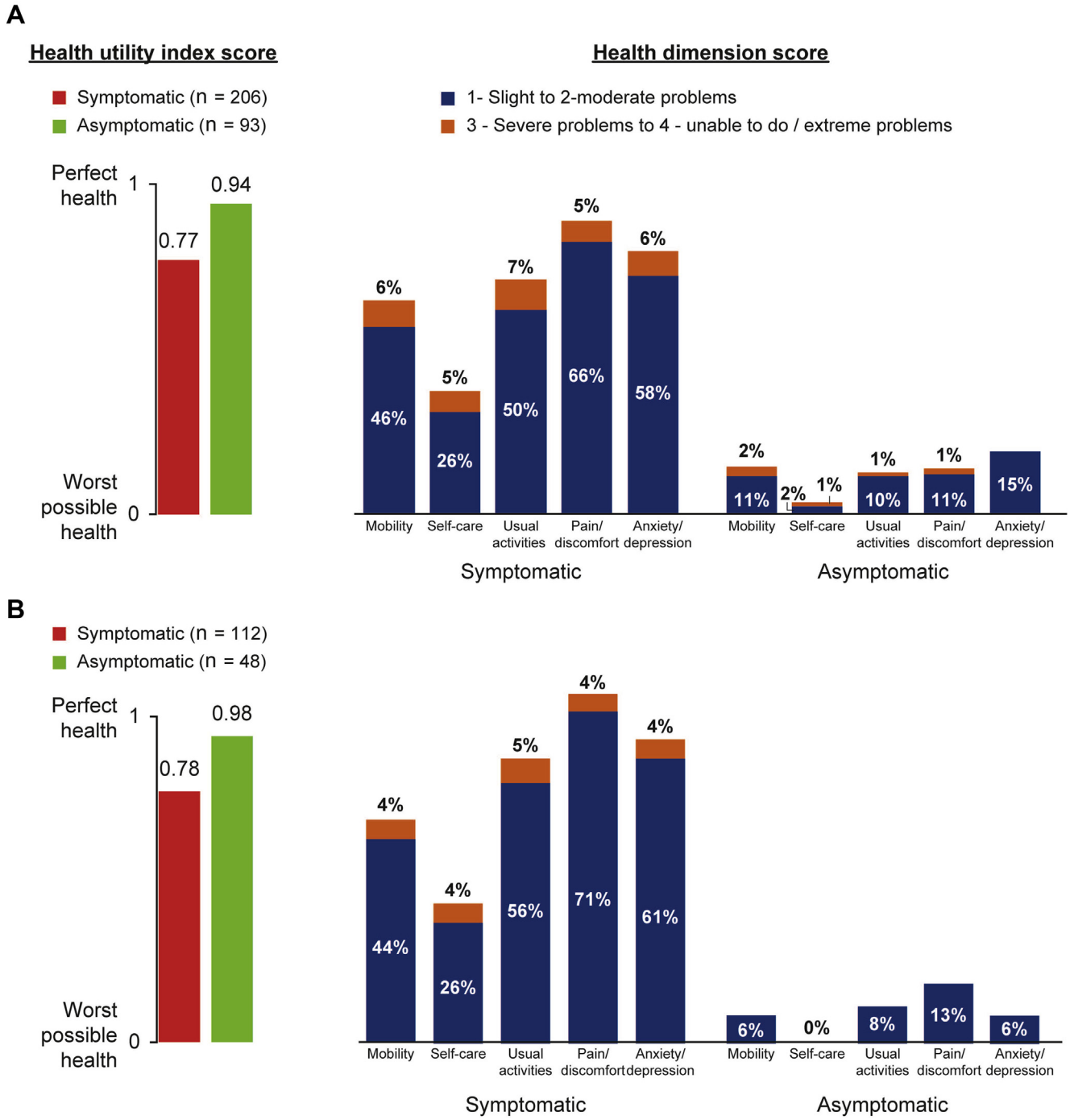
Supplementary Figure 1. Mean number of noninvasive tests (*A*) and procedures (*B*) while under physician management (biopsy-proven patients by fibrosis stage). APRI, aspartate aminotransferase to platelet ratio index; ARFI, acoustic radiation force impulse; CK-18, circulating levels of cytokeratin-18; CT, computed tomography; F, fibrosis stage; GGT, γ-glutamyltransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging.



Supplementary Figure 2. Current nonpharmacologic and pharmacologic interventions reported in the pooled NASH population.



Supplementary Figure 3. Annual mean number of nonroutine health care resource use across countries. ER, emergency room; ICU, intensive care unit.



Supplementary Figure 4. EQ-5D-5L health utility score and health dimension results (*A*) pooled symptomatic versus asymptomatic (*B*) biopsy-proven symptomatic versus asymptomatic cohorts.

Supplementary Table 1. Patient Demographics and Medical Records Data (Biopsy-Confirmed and Fibrosis Stage)

Patient demographics	Biopsy-confirmed (n = 786)	Fibrosis stage 1 (n = 175)	Fibrosis stage 2 (n = 278)	Fibrosis stage 3 (n = 211)	Fibrosis stage 4 (n = 47)
Age, *y* (mean, SD)	54.6 (11.8)	53.6 (12.4)	54.7 (11.9)	55.3 (11.0)	58.0 (10.1)
Male, n (%)	443 (56.4)	90 (51.0)	162 (58.3)	112 (53.1)	32 (68.1)
Female, n (%)	343 (43.6)	85 (48.6)	116 (41.7)	99 (46.9)	15 (31.9)
Ethnicity[a], n (%)	n = 682	n = 164	n = 229	n = 182	n = 34
White	428 (62.8)	115 (70.1)	140 (61.1)	116 (63.7)	20 (58.8)
Hispanic/Latino	104 (15.2)	21 (12.8)	38 (16.6)	30 (16.5)	9 (26.5)
Black African/Black Caribbean/African American	70 (10.3)	15 (9.1)	25 (10.9)	19 (10.4)	3 (8.8)
Other	60 (8.8)	11 (6.7)	25 (10.9)	16 (8.8)	2 (5.9)
Unknown	20 (2.9)	2 (1.2)	1 (0.4)	1 (0.5)	0 (0.0)
Clinical trial enrollment status, n (%)					
Yes, therapeutic interventional study	40 (5.1)	5 (2.9)	17 (6.1)	13 (6.2)	1 (2.1)
Yes, longitudinal, observational study	76 (9.7)	13 (7.4)	31 (11.2)	25 (11.8)	4 (8.5)
No	670 (85.2)	157 (89.7)	230 (82.7)	173 (82.0)	42 (89.4)
Body mass index					
Body mass index, mean (SD)	31.2 (6.9)	30.5 (7.0)	30.7 (5.9)	32.7 (7.8)	33.9 (6.9)
Underweight (<18.5), n (%)	2 (0.3)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Normal/healthy weight (18.5–24.9), n (%)	111 (14.1)	33 (18.9)	40 (14.4)	18 (8.5)	1 (2.1)
Overweight (25.0–29.9), n (%)	268 (34.1)	62 (35.4)	99 (35.6)	64 (30.3)	14 (29.8)
Obese (30.0–34.9), n (%)	228 (29.0)	44 (25.1)	88 (31.7)	65 (30.8)	16 (34.0)
Morbidly obese (>35.0), n (%)	177 (22.5)	36 (20.6)	51 (18.3)	62 (29.4)	16 (34.0)
Fibrosis stage at NASH diagnosis, n (%)					
No fibrosis	55 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fibrosis stage 1 (F1)	175 (22.3)	175 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fibrosis stage 2 (F2)	278 (35.4)	0 (0.0)	278 (100.0)	0 (0.0)	0 (0.0)
Fibrosis stage 3 (F3)	211 (26.8)	0 (0.0)	0 (0.0)	211 (100.0)	0 (0.0)
Fibrosis stage 4 (F4)	47 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)	47 (100.0)
Unknown stage of fibrosis	20 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosed comorbidities (≥10%), n (%)					
Presence of comorbidities	296 (37.7)	53 (30.3)	92 (33.1)	103 (48.8)	28 (59.6)
Type 2 diabetes	184 (62.2)	29 (54.7)	57 (62.0)	68 (66.0)	20 (71.4)
Obesity	151 (51.0)	23 (43.4)	53 (57.6)	51 (49.5)	13 (46.4)
Hypertension	142 (48.0)	24 (45.3)	38 (41.3)	54 (52.4)	15 (53.6)
Dyslipidemia	123 (41.6)	19 (35.8)	39 (42.4)	51 (49.5)	9 (32.1)
Sleep apnea	42 (14.2)	4 (7.5)	16 (17.4)	11 (10.7)	8 (28.6)
Depression	34 (11.5)	5 (9.4)	11 (12.0)	11 (10.7)	3 (10.7)
Coronary arterial disease	17 (5.7)	2 (3.8)	6 (6.5)	7 (6.8)	2 (7.1)

Supplementary Table 1. Continued

Patient demographics	Biopsy-confirmed (n = 786)	Fibrosis stage 1 (n = 175)	Fibrosis stage 2 (n = 278)	Fibrosis stage 3 (n = 211)	Fibrosis stage 4 (n = 47)
Top 5 symptoms at initial presentation, n (%)					
Asymptomatic	521 (66.3)	123 (70.3)	184 (66.2)	127 (60.2)	24 (51.1)
Fatigue	153 (19.5)	29 (16.6)	53 (19.1)	52 (24.6)	12 (25.5)
Abdominal bloating or swelling	117 (14.9)	22 (12.6)	37 (13.3)	43 (20.4)	11 (23.4)
Abdominal pain or discomfort	116 (14.8)	24 (13.7)	43 (15.5)	34 (16.1)	11 (23.4)
Malaise	102 (13.0)	26 (14.9)	40 (14.4)	23 (10.9)	8 (17.0)

NASH, nonalcoholic steatohepatitis; SD, standard deviation.
[a]Ethnicity data could not be collected for patients from France

Supplementary Table 2. Diagnostic and Monitoring Tests in Pooled and Biopsy-Confirmed Population

	Pooled cohort (N = 1216)			Biopsy-confirmed (n = 786)		
	Diagnosis, n (%)	Monitoring, n (%)	Mean number (SD)	Diagnosis, n (%)	Monitoring, n (%)	Mean number (SD)
Liver biopsy	802 (66.0)	141 (11.6)	1.2 (0.7)	786 (100)	131 (16.7)	1.2 (0.7)
Ultrasound	760 (62.5)	662 (54.4)	2.7 (2.3)	464 (59.0)	450 (57.3)	2.9 (2.5)
Acoustic radiation force impulse imaging	27 (2.2)	30 (2.5)	1.5 (1.2)	19 (2.4)	27 (3.4)	1.6 (1.2)
Computed tomography scan	197 (16.2)	100 (8.2)	1.4 (0.8)	135 (17.2)	75 (9.5)	1.5 (0.8)
Magnetic resonance imaging	115 (9.5)	72 (5.9)	1.5 (1.2)	71 (9.0)	50 (6.0)	1.7 (1.4)
Magnetic resonance elastography	55 (4.5)	39 (3.2)	1.7 (1.1)	39 (5.0)	30 (3.8)	1.8 (1.3)
FibroScan, 2-dimension transient elastography	282 (23.2)	256 (21.1)	2.0 (1.4)	138 (17.6)	143 (18.2)	2.1 (1.5)
Serum transaminases (AST, ALT)	794 (65.3)	784 (64.5)	5.0 (4.0)	486 (61.8)	484 (61.6)	5.0 (4.2)
γ-Glutamyl transferase	532 (43.8)	466 (38.3)	4.7 (3.6)	323 (41.1)	305 (38.8)	5.0 (3.9)
FibroTest/FibroSure	238 (19.6)	192 (15.8)	2.0 (1.4)	137 (17.4)	128 (16.3)	2.2 (1.3)
Fibrosis-4 Index	75 (6.2)	76 (6.3)	2.3 (1.6)	52 (6.6)	61 (7.8)	2.3 (1.7)
AST to platelet ratio index	250 (20.6)	212 (17.4)	3.5 (2.6)	170 (21.6)	146 (18.6)	3.4 (2.7)
Steatosis, activity, and fibrosis score	98 (8.1)	72 (5.9)	2.0 (1.4)	70 (8.9)	49 (6.2)	1.9 (1.3)
NashTest	116 (9.5)	96 (7.9)	1.7 (1.3)	80 (10.2)	73 (9.3)	1.8 (1.4)
NAFLD fibrosis score	180 (14.8)	138 (11.3)	2.5 (2.1)	122 (15.5)	102 (12.9)	2.4 (2.2)
NAFLD activity score	193 (15.9)	167 (13.7)	2.6 (2.8)	147 (18.7)	125 (15.9)	2.6 (2.8)
Enhanced liver fibrosis panel score	48 (3.9)	48 (3.9)	2.0 (1.3)	27 (3.4)	34 (4.3)	1.9 (1.3)
Circulating levels of cytokeratin-18	53 (4.4)	49 (4.0)	2.4 (1.5)	41 (5.2)	42 (5.3)	2.6 (1.6)
Lipid profile (cholesterol, LDL, HDL, and triglycerides)	600 (49.3)	454 (37.3)	4.1 (3.6)	371 (47.2)	310 (39.4)	4.1 (3.6)
Platelet count	540 (44.4)	491 (40.4)	5.0 (4.2)	340 (43.3)	335 (42.6)	5.0 (4.0)
Clotting studies (prothrombin time, international normalized ratio)	403 (33.1)	329 (27.1)	4.4 (4.0)	274 (34.9)	229 (29.1)	4.4 (3.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.

Supplementary Table 3. Diagnostic and Monitoring Tests Across Countries

Tests and procedures used to diagnose or monitor NASH	United States (N = 702)		France (N = 227)		Germany (N = 287)	
Diagnosis, n (%)						
Liver biopsy	506	72.1%	107	47.1%	189	65.9%
US	443	63.1%	153	67.4%	164	57.1%
ARFI imaging	13	1.9%	3	1.3%	11	3.8%
CT scan	135	19.2%	21	9.3%	41	14.3%
MRI	50	7.1%	22	9.7%	43	15.0%
MRE	30	4.3%	8	3.5%	17	5.9%
FibroScan, 2-dimension transient elastography	90	12.8%	124	54.6%	68	23.7%
Serum transaminases (AST, ALT)	451	64.2%	165	72.7%	178	62.0%
GGT	206	29.3%	159	70.0%	167	58.2%
FibroTest/FibroSure	110	15.7%	91	40.1%	37	12.9%
FIB-4	40	5.7%	13	5.7%	22	7.7%
APRI	159	22.6%	42	18.5%	49	17.1%
SAF	58	8.3%	14	6.2%	26	9.1%
NashTest	37	5.3%	30	13.2%	49	17.1%
NFS	101	14.4%	30	13.2%	49	17.1%
NAS	110	15.7%	22	9.7%	61	21.3%
ELF	23	3.3%	1	0.4%	24	8.4%
CK-18	17	2.4%	6	2.6%	30	10.5%
Lipid profile (cholesterol, LDL, HDL, and triglycerides)	302	43.0%	132	58.1%	166	57.8%
Platelet count	278	39.6%	136	59.9%	126	43.9%
Clotting studies (PT, INR)	198	28.2%	74	32.6%	131	45.6%
Monitoring, n (%)						
Liver biopsy	92	13.1%	6	2.6%	43	15.0%
US	377	53.7%	111	48.9%	174	60.6%
ARFI imaging	15	2.1%	3	1.3%	12	4.2%
CT scan	69	9.8%	4	1.8%	27	9.4%
MRI	34	4.8%	9	4.0%	29	10.1%
MRE	11	1.6%	7	3.1%	21	7.3%
FibroScan, 2-dimension transient elastography	82	11.7%	112	49.3%	62	21.6%
Serum transaminases (AST, ALT)	450	64.1%	157	69.2%	177	61.7%
GGT	160	22.8%	141	62.1%	165	57.5%
FibroTest/FibroSure	89	12.7%	66	29.1%	37	12.9%
FIB-4	42	6.0%	9	4.0%	25	8.7%
APRI	131	18.7%	23	10.1%	58	20.2%
SAF	40	5.7%	9	4.0%	23	8.0%
NashTest	37	5.3%	12	5.3%	47	16.4%
NFS	65	9.3%	21	9.3%	52	18.1%
NAS	81	11.5%	19	8.4%	67	23.3%
ELF	25	3.6%	1	0.4%	22	7.7%
CK-18	20	2.8%	5	2.2%	24	8.4%
Lipid profile (cholesterol, LDL, HDL, and triglycerides)	214	30.5%	72	31.7%	168	58.5%
Platelet count	265	37.7%	103	45.4%	123	42.9%
Clotting studies (PT, INR)	161	22.9%	44	19.4%	124	43.2%
Mean (SD) number						
Liver biopsy	1.2	0.8	1.1	0.5	1.2	0.5
US	2.4	2.4	2.5	1.4	3.7	2.5
ARFI imaging	1.5	1.0	1.0	1.2	1.8	1.3
CT scan	1.4	0.8	1.6	0.9	1.4	0.8
MRI	1.6	1.4	1.5	0.7	1.6	1.0
MRE	1.6	1.2	1.6	1.0	1.9	1.1
FibroScan, 2-dimension transient elastography	2.0	1.6	2.1	1.3	2.0	1.1
Serum transaminases (AST, ALT)	4.7	4.2	5.3	3.2	5.4	4.2
GGT	3.8	3.6	5.1	3.1	5.5	3.9
FibroTest/FibroSure	2.0	1.4	2.3	1.5	1.7	1.1
FIB-4	2.4	1.8	2.8	1.7	1.9	1.2
APRI	3.6	2.8	3.1	2.0	3.3	2.1
SAF	1.7	1.2	3.0	1.1	2.2	1.6
NashTest	2.0	1.8	1.5	0.7	1.6	0.9
NFS	2.7	2.4	2.7	1.6	1.8	1.2
NAS	2.8	3.1	2.8	3.6	2.3	1.5

Supplementary Table 3. Continued

Tests and procedures used to diagnose or monitor NASH	United States (N = 702)		France (N = 227)		Germany (N = 287)	
ELF	2.1	1.3	2.0	1.4	1.8	1.3
CK-18	2.3	2.0	2.5	1.2	2.5	1.3
Lipid profile (cholesterol, LDL, HDL, and triglycerides)	3.4	3.4	4.3	3.0	5.1	4.0
Platelet count	4.8	4.8	5.1	3.3	5.2	3.6
Clotting studies (PT, INR)	4.0	4.6	4.4	2.9	4.8	3.6

ALT, alanine aminotransferase; APRI, AST to platelet ratio index; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; CK-18, circulating levels of cytokeratin-18; CT, computed tomography; ELF, enhanced liver fibrosis panel score; FIB-4, Fibrosis-4 Index; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; PT, prothrombin time; SAF, steatosis, activity, and fibrosis score; SD, standard deviation; US, ultrasound.

Supplementary Table 4. Patient-Reported Outcome Results (Pooled Population)

Outcome measure	Pooled cohort
Mean CLDQ score ± SD	5.10 ± 1.43
Mean EQ-5D-5L score ± SD	0.83 ± 0.21
WPAI-NASH	
% Absenteeism ± SD	9.0 ± 22.5
% Presenteeism ± SD	17.5 ± 19.9
% Overall work impairment ± SD	24.7 ± 27.4
% Activity impairment ± SD	30.7 ± 28.5

CLDQ, Chronic Liver Disease Questionnaire; NASH, nonalcoholic steatohepatitis; SD, standard deviation; WPAI, Work Productivity and Activity Impairment.