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The Economic and Clinical Burden of Non-alcoholic Fatty Liver Disease (NAFLD) in the United States and Europe

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NAFLD; NASH; costs; quality of life; burden of illness; economic burden

List of Abbreviations

Non-alcoholic fatty liver disease **(**NAFLD)

United States of America (USA)

Non-alcoholic fatty liver (NAFL)

Non-alcoholic steatohepatitis (NASH)

Diabetes mellitus (DM)

Hepatocellular carcinoma (HCC)

Liver transplantation (LT)

Short form-36 (SF-36)

Chronic Liver Disease Questionnaire (CLDQ)

4 European countries (EU-4).

France (FRA)

United Kingdom (UK)

Germany (GER)

Italy (ITA)

Non-alcoholic fatty liver (NAFL)

Non-cirrhotic (NC)

No fibrosis (No FB)

Fibrosis (FB) sub-states)

Compensated cirrhosis (CC)

Decompensated cirrhosis (DCC)

Hepatocellular carcinoma (HCC)

Liver transplant (LT)

Post-liver transplant (PLT)

Relative risk (RRs)

United Nation of Organ Sharing (UNOS)

National Health and Nutrition Examination Survey (NHANES)

Generalized Reduced Gradient (GRG)

Hepatitis C virus (HCV)

Abstract:

BACKGROUND AND AIM: Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease. There is uncertainty around the economic burden of NAFLD. We constructed a steady-state prevalence model to quantify this burden in the United States of America (USA) and Europe (EU).

METHODS: Five models were constructed estimating burden of NAFLD in the USA and 4 European countries. Models were built using a series of interlinked Markov chains, each representing age increments of the NAFLD and the general population. Incidence and remission rates were calculated by calibrating against real-world prevalence rates. The data was validated using a computerized disease Model called DisMod II. NAFLD patients transitioned between nine health states (nonalcoholic fatty liver, non-alcoholic steatohepatitis (NASH), NASH-fibrosis, NASH-compensated cirrhosis, NASH-decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, post-liver transplant and death). Transition probabilities were sourced from the literature, systematic review and was calibrated against real-world data. Utilities were obtained from NAFLD patients using SF-6D. Costs were sourced from the literature and local fee schedules.

RESULTS: In the USA, over 64 million people are projected to have NAFLD, with annual direct medical costs of about $103 bn [$1,613 per patient (PP)]. In EU-4 countries [Germany, France, Italy and United Kingdom], there are ~52 million people with NAFLD with an annual cost of about € 35 billion (from € 354 to € 1,163 PP). Costs are highest in patients aged 45-65. The burden is significantly higher when societal costs are included.

CONCLUSION:

The analysis quantifies the enormity of the clinical and economic burden of NAFLD, which will likely increase as incidence of NAFLD continues to rise.

Introduction:

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease. In a recent systematic review, the global prevalence of NAFLD was estimated to be approximately 24% [1]. NAFLD is predominantly associated with obesity and type 2 diabetes [1]. In addition to the United States of America (USA) and Europe, high prevalence rates of obesity have also been reported from South America, Asia, and Middle East [1,2].

In order to fully understand the clinical burden of NAFLD, it is important to recognize the full spectrum of NAFLD phenotype [2]. Histologically, the potentially progressive form of NAFLD has been referred to as non-alcoholic steatohepatitis (NASH) [2]. Although NASH represents the minority (10-20%) of patients with NAFLD, the non-alcoholic steatohepatitis (NASH) subtype can potentially progress to advanced liver disease leading to cirrhosis, liver-related mortality and hepatocellular carcinoma (HCC) [1-5]. Despite NASH being a more progressive type of NAFLD, the non-NASH type of NAFLD still carries clinical burden as it is associated with cardiovascular diseases and complications [6].

Clinically, NASH seems to be more common and potentially more progressive in the setting of insulin resistance and diabetes mellitus (DM) [7]. Other studies have also shown that DM is an independent predictor of advanced fibrosis and long-term mortality in NAFLD [8-9]. In addition, the presence of advanced fibrosis (stage>2) in NAFLD has been associated with increased liver-related mortality [10-11]. These data, therefore, may be an indicator that grade of fibrosis is a surrogate for predicting liver related mortality.

In addition to cirrhosis, there is mounting evidence that NAFLD is an important risk factor for HCC [12-13]. Although cirrhosis in NASH has been indicated as a risk factor for HCC, there is some evidence to suggest that non-cirrhotic patients with NAFLD may also be at risk of developing HCC [14]. Finally, the clinical outcome of NAFLD has led to a large number of liver transplants (LTs) in the United States. In fact, NASH is now considered the second most common indication for LT in the USA after chronic hepatitis C, and is growing [15].

In addition to its clinical impact, NAFLD has an impact on patient-reported outcomes [16]. In fact, recent data suggest that NAFLD patients may have a significant impairment of their physical health as measured by two patient-reported quality of life measurement tools, namely, the Short Form-36 (SF-36) and the Chronic Liver Disease Questionnaire (CLDQ) [17]. Finally, NAFLD has been shown to have an important economic impact on healthcare utilization [16]. In a recent study of Medicare NAFLD patients, the mean yearly inflation-adjusted charges from the outpatient setting increased from $2624±$3308 in 2005 to $3608±$5132 in 2010 in dollars of 2010 [18]. In a follow-up study of both outpatient and inpatient Medicare resource utilization, the enormous impact of NAFLD was reiterated and the median total hospital charges for NAFLD patients was $36,289 in 2010 [19].

In the context of growing clinical and quality of life burden of NAFLD, the economic burden of this important liver disease for the USA and Europe is likely to increase. Therefore, our aim is to estimate the clinical and economic burden of NAFLD in the USA and four European countries using a decision analytic Markov-based model.

Study Data and Methods

Model Structure and Assumptions

Five separate models were constructed to estimate the clinical and economic burden of NAFLD in the U.S. and 4 European countries (EU-4). The four EU countries included France (FRA), United Kingdom (UK), Germany (GER), and Italy (ITA).

Each model was constructed using a series of interlinked Markov chains in Microsoft Excel spreadsheets, using the general structure as in Figure 1, which depicts a Markov model for the general population. Within the general population, individuals were classified into four possible states: susceptible; NAFLD; NAFLD-specific deaths; and all-cause deaths. Individuals transition probabilities between these states were calculated by applying incidence, remission, mortality and NAFLD-specific mortality rates [1-15].

As NAFLD is a progressive disease, an embedded disease-specific Markov structure allowed for patients with NAFLD to transition to different liver disease health states: non-alcoholic fatty liver (NAFL) (with no progression), non-cirrhotic (NC) NASH (with no fibrosis (No FB) and fibrosis (FB) sub-states) which could progress to compensated cirrhosis (CC); decompensated cirrhosis (DCC); hepatocellular carcinoma (HCC); liver transplant (LT); post-liver transplant (PLT); and, death. The remission rate was applied only to those in the NAFL health state and case fatality was applied using the transition probabilities to death from DCC, HCC, LT, and PLT. While remission was only allowed in the NAFL health state, regression was permitted from CC to FB, FB to No FB and No FB to FB therefore patients could indirectly transition from these health states to the general population [1-15, 20-31].

Using this framework, the number of cases in each of the liver disease states was estimated by following a susceptible cohort over time and applying the transition probabilities as described below. Cohorts of patients were followed in five year bands. It is important to note including patients aged under 20 may introduce confounding due to those with potential inherited metabolic disorders associated with early NAFLD; however, this population was still included for completeness of the model. The prevalence of each disease state at a certain age was calculated by applying the incidence, mortality, and disease transition probabilities to the prevalent population of the previous age. As such, under the conditions of static incidence, mortality, and disease transition probabilities with respect to time, a patient's age is equal to the cycle number of the model and the model is at steady state [1-15, 20-31]

Clinical Inputs

Different age intervals were used for the clinical inputs within the model; country-specific background mortality rates were applied in five year intervals and were sourced from publically available databases (**Supplementary table 1)** [20-21]. Incidence rates were applied in five year intervals and calculated using the calibration method described below; five-year age bands were selected for these parameters as they were not expected to vary significantly within these bands [20-21].

Given the limited amount of data available for the age-specific natural history of NAFLD, a base transition matrix without regard to age was built from the published literature (**Supplementary table 2**) [22-31]; where data gaps existed, values were imputed from the primary sources used in a recent cost-effectiveness analysis of patients with hepatitis C [32]. These probabilities were then varied over four distinct age bands (<20, 20-44, 45-64, and 65+) by applying relative risks (RR) to the base transition matrix. The age-specific RRs for all progressive transition probabilities with the exception of transition to liver transplant were based on risk of death post-liver transplant obtained from the United Nation of Organ Sharing (UNOS) database (**Supplementary table 3**) [30,31]. The RRs for probability of LT were calculated by adjusting for the number of LTs due to NAFLD by age relative to all the LTs due to NASH in the USA in 2014, as sourced from UNOS **(Supplementary table 3)** [30,31].

Gender-specific adult NAFLD prevalence rates for the USA were obtained from the National Health and Nutrition Examination Survey III (NHANES III) database across the four age bands included in the model and adjusted using a relative risk (RR) factor of 1.45 to reflect the difference between these prevalence rates and the rates reported in a recent meta-analysis [1,31]. These prevalence rates were assumed to be the same in Europe as prevalence rates were reported to be similar [1].

Utilities were obtained directly from NAFLD patients using SF-6D scores (**Supplementary table 3).**

Costing Inputs

In the model's base case, both direct medical costs and societal costs were considered. Conservatively, additional costs due to the presence of comorbid conditions (e.g. treatment costs, complication costs) were not modelled.

Annual costs of each health state at a macro level were sourced from recent publications (**Supplementary table 4**) [33-38]. Costs for patients in lesser-progressed model health states were micro-costed using resource utilization inputs from hepatology experts mapped to national fee schedules. For the USA analysis, annual hospitalization costs for NAFLD without cirrhosis were obtained from a recent Medicare cost analysis [18-19], and those costs were assumed to apply across all NAFL and non-cirrhotic NASH health states. Hospitalization costs were adjusted for European markets using an adjustment factor.

Societal costs were calculated by estimating the annual quality-adjusted life years (QALYs) lost due to NAFLD and by applying a monetary value to this QALY estimate. QALYs were measured by assigning utility scores of between 1 (perfect health) and 0 (death) to each NAFLD health state, and multiplying the utility scores by survival, weighted by health state. QALYs lost were calculated as the difference between the projected QALYs in the NAFLD population and the projected QALYs in the general population, weighted by age, as sourced from the National Health Measurement study [31, 39-45]. This difference was then multiplied by the monetary value of a QALY. Monetary values were assigned using thresholds at which payers are willing to pay for additional QALYs gained for new interventions. In the USA, interventions are typically accepted as being cost-effective where the cost per additional QALY gained is less than $50,000 to $150,000, but there have been calls for this value to be set much higher, valuing QALYs at up to $300,000. In the UK, interventions are accepted as cost-effective if the cost per QALY gained is less than £30,000, or £50,000 where the intervention is classified as end-of-life care. In Europe, willingness-to-pay thresholds are less commonly used to make reimbursement decisions but interventions are typically accepted as cost-effective where the value per QALY gained ranges between €75,000 and €125,000. In our analysis, the values per QALY gained were therefore set at $50,000 (USA), €75,000 (GER, FRA, ITA), and £30,000 (UK) in the base case. The utility scores were obtained in patients with NAFLD **(Supplementary table 5**) [16, 29,43-45].

Model Validation

The outer Markov model was validated using DisMod II, a generic mathematical disease model published by the World Health Organization (Table1) [46-48]. DisMod II numerically solves a set of linear differential equations that describe the transitions between states as represented in **Figure 1** using a finite differences method. DisMod II is able to calculate incidence rates from given prevalence, general mortality, remission and relative risk mortality data. The remission rate was assumed to be 20%, an estimate provided by a panel of hepatologists. The RR for NAFLD excess mortality by age was obtained from the NHANES database adjusted using a RR factor as described above. Within DisMod II, a polynomial curve was fitted to the prevalence data sourced from NHANES for four age bands, and the incidence rates which were calculated by DisMod II were used as inputs

into our model. An additional validation step compared (via visual inspection) the NAFLD prevalence rates generated by our model versus those generated by DisMod II **(Supplementary Figure 1)**.

Model Calibration

Using the global criterion method [48], the model was calibrated against several empirical real-world data targets, which were obtained from the literature (**Supplementary table 6)** [23, 30-32,47,49]. The calibration procedure used the Generalized Reduced Gradient (GRG) non-linear optimization routine that is available in the SOLVER add-in that comes packaged with Microsoft Excel. Model input parameters were allowed to vary within a set of given constraints (**Table 2**). Calibration factors to the NAFLD incidence rates across the four age bands used in the prevalence calibration targets (**Supplementary table 5)** were applied, which allowed for matching to real world prevalence data rather than the smoothed DisMod II data [33,43-45]. Model residual errors were calculated by subtracting the model output value from the calibration target value. These were squared and summed to provide an objective minimization target. The model's clinical inputs were calibrated for the USA population and applied unchanged to the European countries. The inputs and outputs of the model calibration are provided in **Table 2**.

Sensitivity Analyses

One-way deterministic sensitivity analyses were performed to test the impact of model parameters on results; all model parameters were varied +/- 20%, with the exception of utility values, where inputs from a Hepatitis C virus (HCV) patient population were used as an upper bound, and societal costs, where values of $300,000 (USA), €125,000 (GER, FRA, ITA), and £50,000 (UK) were used.

RESULTS

Model Calibration and Validation

NAFLD incidence rates predicted from DisMod II (24,25) **(Figure 3)** were in line with the few real-world NAFLD incidence estimates available, which range from 2% to 5% according to recent studies [1,4]. Further, when comparing our model's projected NAFLD prevalence to DisMod's calculation based on NHANES data, the two models give similar age-prevalence curves as assessed by visual inspection **(Supplementary Figure 1)**. However, our model slightly under-predicts NAFLD prevalence relative to DisMod II. This is not surprising given the differences between the models, such as the way that case mortality data is estimated and how case remission is applied: in DisMod II, remission and case mortality are applied equally across the NAFLD population, while in our model, remission is only applied in the NAFL health state and case mortality varies by health state, increasing with disease progression.

Upon calibration, our model's outputs were closely matched to multiple USA real-world targets (**Supplementary Table 6**) while keeping input parameters in ranges bound by literature estimates and expert opinion (**Table 2**) [23, 30-32,47,49].

Clinical Burden of Disease

The annual clinical burden of NAFLD is projected to be substantial in both the USA and EU-4. In the USA, over 12 million incident cases of NAFL, and over 600,000 incident cases of NASH are predicted, with proportionally similar results in the EU (**Supplementary table 7**). A significant number of newly progressed cases of cirrhosis, both compensated and decompensated, HCC due to NAFLD, and LT due to NAFLD are also projected (**Supplementary table 7**). Incident cases of disease peak in the 45-64 age group (**Supplementary table 8**).

Trends in projected disease prevalence are similar, with nearly 64 million people in the USA projected to have NAFLD (**Table 3**), with results proportionally similar in the EU-4. The majority of

NAFLD patients (91.3%) have not yet progressed to NASH, given the slow progressive nature of the disease. Prevalent cases of disease peak in the 45-64 age group (**Table 4**).

Economic Burden of Disease

In line with our clinical estimates, the annual economic burden of NAFLD is projected to be substantial in both the USA and the EU-4. The total burden is higher in the USA ($103 billion in direct costs per year) relative to the EU-4 due to the larger population (where it was €27.7 billion in Germany, France and Italy together, and £5.24 in the UK), as well as higher costs of managing disease-related complications, which also increase the per-patient costs (**Table 5**). Total costs were the highest in patients aged 45-65, mirroring the disease prevalence (**Table 6**). However, per patient costs were the highest in the 65+ age group, reflecting the higher proportion of these patients in more advanced stages of disease (data not shown). Accounting for societal costs would significantly increase the total burden of disease in all markets (**Table 5**). The differences in direct economic burden between countries is reflective of the different component costs of care; differences in projected societal burden differences in willingness to pay per QALY gained in these markets.

Sensitivity Analyses

Given that NAFL was the NAFLD patient segment with the highest prevalence relative to more progressed states of NAFLD (NASH with fibrosis, NAFLD CC, DC, HCC and LT), our model was most sensitive to parameters impacting this state, including the rate of remission to a disease-free state, NAFL monitoring costs, and NAFL transition probabilities. As expected, the incident rate of disease was also a significant model driver across all age bands (**Supplementary Figure 2**).

DISCUSSION

This is the most extensive study assessing the economic and clinical burden of NAFLD in the USA and four major European countries. Our model estimates that there are 64 million individuals with NAFLD in the USA and 52 million in the four European countries. Our model also provides an estimate for the number of patients who will develop new cases of NAFLD complications on an annual basis for the USA and EU-4. These analyses suggest that the clinical burden of NAFLD in the USA and EU is tremendous, and is potentially growing.

As the clinical consequences of NAFLD grow, the economic consequences will also increase. Our previous work determined that the discounted lifetime cost of a cohort of incident newly-diagnosed NAFLD patients is $5.8 billion in the USA [29]. Our current work extends these findings, estimating the annual burden associated with all incident and prevalent NAFLD in the US at $103 billion, and €35 billion for the EU-4 countries – in line with estimates of the economic burden associated with diabetes and heart disease [50]. Using standard discounting assumptions, this would result in a 10-year economic burden of NAFLD of $908 and €302 billion, respectively, in the USA and EU-4, assuming a constant incidence of disease. However, if we assume the annual rate of increase in the costs due to NAFLD to parallel the annual growth in the prevalence of obesity in the USA since 1994 [51], the expected 10-year burden of NAFLD could increase substantially – to an estimated $1,005 billion in the US and €334 billion in the EU-4.

In addition to direct annual cost of NAFLD, there is also a societal cost related to the loss of QALYs due to NAFLD and its complications. By assigning a monetary value to societal costs and adding these to the annual direct cost of NAFLD for the USA and EU-4, the total annual cost of NAFLD can be estimated at $292.19 billion and €227.84 billion, respectively. Furthermore, these cost calculations do not take into account other indirect costs of NAFLD which are related to work productivity loss and its economic impact. Treatment costs were not included in this model, as, unlike for viral hepatitis and other etiologies of chronic liver disease, there are currently no effective therapies

approved for the treatment of NAFL or NASH. However, as there are a significant number of therapies currently under investigation [52], this may substantially change the cost burden of NAFLD in the future.

Our model structure was designed to comprehensively project NAFLD burden of disease by simulating movement between the diseased and non-diseased populations via incidence, progression and remission/regression across multiple patient age bands via interlinking Markov chains. However, our analysis is subject to several limitations. First, an inherent assumption of using a steady-state model is that we assume that the incidence and prevalence have reached a steady state; our results may, therefore, underestimate the true future burden of NAFLD, particularly in older age groups where the impact of changing incidence has not yet been realized. Additionally, substantial uncertainty around many inputs existed, particularly the NAFLD incidence and the rates of fibrosis progression; further research is required to validate these parameters, although we calibrated the most uncertain inputs within an appropriate range to approach real-world targets and, thus, believe that the impact of this on our model results is not substantial. Further, the model was calibrated using the real-world prevalence data for the USA and assumed the same incidence and disease progression across the EU-4. The impact of this approach is expected to be minimal given that European NAFLD prevalence rates were reported to be similar to the USA [1]. Finally, most of the studies included in this analysis focused on individuals with NAFLD alone, which does not consider that concurrent NAFLD can also occur among patients with co-existing liver disease etiologies, specifically, chronic HBV and chronic HCV. This cost could not be quantified in this analysis given the lack of complete data about super-impose NAFLD on other types of chronic liver disease. . However, if these costs had been included, the clinical and economic burden of NALFD projected by our model would certainly be significantly increased.

In summary, this is the first comprehensive model estimating the clinical and economic burden of NAFLD. Despite the enormous economic burden estimated by this analysis, it is most likely that we have underestimated the economic burden of the disease due to conservative assumptions related to the clinical burden and the disease progression rates. Nevertheless, our analysis provides an economic basis to appreciate the actual burden of NAFLD, NASH, and their complications to the society. Given the epidemic of NAFLD, understanding the full burden of NAFLD will help providers, payers, and policy makers to develop strategies to identify high risk patients with NAFLD and to implement a multi-prong public heath policy to deal with this important chronic liver disease.

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Table 1: The DisMod inputs and outputs.

AGE BAND	DISMOD INPUT (RATE)		SOURCE
	MALE	FEMALE	
NAFLD PREVALENCE			
0-9	0	0	Assumption
10-19	0.0960	0.0960	Schwimmer 2008[44]
20-44	0.1960	0.1586	NHANES database (adjusted*)[31]
45-64	0.3573	0.304	NHANES database (adjusted*)[31]
65+	0.3486	0.3022	NHANES database (adjusted*)[31]
NAFLD REMISSION			
0-84	20%	20%	Assumption
RELATIVE RISK MORTALITY FOR NALFD VS. GENERAL POPULATION			
0-19	1.00	1.00	Assumption
20-44	1.27	1.27	NHANES database[31]
45-64	1.10	1.10	NHANES database[31]
65+	1.00	1.00	NHANES database[31]
DISMOD OUTPUT: NAFLD INCIDENCE (RATE)			
0-4	0.0019	0.0017	DISMOD
5-9	0.0139	0.0124	DISMOD
10-14	0.0251	0.0214	DISMOD
15-19	0.0338	0.0279	DISMOD
20-24	0.0445	0.0365	DISMOD
25-29	0.0538	0.0436	DISMOD
30-34	0.0632	0.0509	DISMOD
35-39	0.0724	0.058	DISMOD
40-44	0.0811	0.0645	DISMOD
45-49	0.0887	0.0703	DISMOD
50-54	0.0954	0.0759	DISMOD
55-59	0.0991	0.0806	DISMOD
60-64	0.1	0.0844	DISMOD
65-69	0.1	0.0874	DISMOD
70-74	0.1	0.0893	DISMOD
75-79	0.1	0.0902	DISMOD
80-84	0.1	0.0898	DISMOD
85-89	0.1	0.0884	DISMOD
90-94	0.1	0.0865	DISMOD
95+	0.1	0.0856	DISMOD

*The prevalence rates reported in the NHANES database were adjusted to account for the higher prevalence rates reported in a recent meta-analysis[1] using a RR of 1.45 (0.2413/0.1623)

Table 2: Calibrated inputs.

	DEFAULT INPUT	CALIBRATION RANGE	CALIBRATED INPUT
Incidence rate adjustment			
<20	1.00	0.5 to 1.5	1.15
20-44	1.00	0.5 to 1.5	0.71
45-64	1.00	0.5 to 1.5	0.99
65+	1.00	0.5 to 1.5	0.88
Rate of remission to disease-free	20%	16% to 24%	19%
Transition probabilities			
NAFL to NASH no FB	0.98%	0.20% to 6.00%	0.83%
NASH no FB to FB	5.23%	5.00% to 10.00%	5.00%
NASH FB to CC	5.23%	5.00% to 10.00%	5.00%
NASH CC to DCC	3.90%	3.00% to 4.80%	3.71%
NAFL to HCC	0.04%	0.00% to 0.08%	0.00%
NASH NC to HCC	0.04%	0.01% to 0.08%	0.03%
NASH CC to HCC	2.60%	0.5% to 4.0%	0.52%
Regression from NASH-no FB	5.23%	0.00% to 6.00%	5.64%
Regression from FB and CC states	5.93%	0.00% to 6.00%	6.00%
DCC to LT	3.10%	2.60% to 3.60%	2.84%
HCC to LT	3.10%	3.10% to 23.00%	3.06%
DCC to EM	12.90%	10.00% to 20.00%	14.23%
HCC to EM	62.00%	50.00% to 70.00%	62.24%
Fibrosis progression			
<20	0.48	0.25 to 0.5	0.48
20-44	0.73	0.5 to 0.75	0.50
45-64	0.97	0.9 to 1.2	0.90
65+	1.21	1.2 to 1.6	1.20

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant; EM, extra mortality

Table 3: Annual predicted prevalent cases of NAFLD.

	USA	Germany	France	Italy	UK
NAFLD	64,082,827	12,250,944	14,545,923	10,271,816	14,678,931
NAFL	58,538,434	11,087,128	13,107,353	9,268,326	13,265,903
NASH FB	3,705,092	748,959	911,952	639,539	905,022
NASH FB	1,316,505	288,548	362,748	251,633	352,273
NASH CC	436,896	104,681	135,514	92,965	128,976
NASH DCC	70,766	18,125	23,875	16,261	22,451
HCC	5,848	1,370	1,760	1,211	1,684
LT	859	190	238	165	232
PLT	8,428	1,944	2,482	1,715	2,391

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant

Table 4: Annual predicted prevalent cases of NAFLD by age group (USA).

	<20	20-44	45-64	65+
NAFL	4,560,491	15,603,583	20,160,223	18,214,137
NASH NO FB	82,330	615,658	1,228,805	1,778,299
NASH FB	6,257	113,026	359,200	838,022
NASH CC	373	15,531	86,450	334,541
NASH DCC	26	1,872	10,958	57,910
HCC	34	356	1,246	4,212
LT	1	59	415	384
PLT	3	298	2,363	5,764
TOTAL	4,649,516	16,350,383	21,849,659	21,233,269

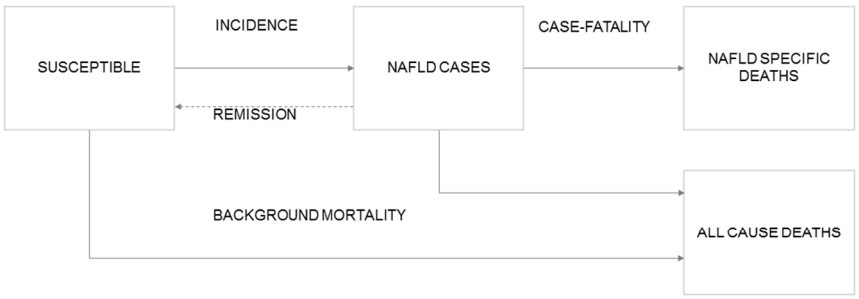
Table 5: Annual predicted economic burden of NAFLD by country.

	USA	GER	FRA	ITA	UK
Total costs (in billions)					
Direct costs	$ 103.31	€ 4.33	€ 11.40	€ 11.95	£5.24
Societal costs	$ 188.88	€ 51.94	€ 64.31	€ 44.14	£26.03
Total costs	$ 292.19	€ 56.27	€ 75.72	€ 56.09	£31.26
Total costs (per patient)					
Direct costs	$ 1,612.18	€ 354	€ 784	€ 1,163	£357
Societal costs	$ 2,947.36	€ 4,240	€ 4,421	€ 4,297	£1,773
Total costs	$ 4,559.54	€ 4,593	€ 5,205	€ 5,460	£2,130
Costs (in millions) due to					
NAFL	$ 86,564.2	€ 3,492.43	€ 9,163.92	€ 9,776.54	£4,326.86
NASH NO FB	$ 5,483.6	€ 244.07	€ 759.79	€ 701.42	£301.79
NASH FB	$ 1,866.3	€ 87.86	€ 242.90	€ 250.94	£110.21
CC	$ 6,573.3	€ 312.74	€ 916.78	€ 900.07	£362.66
DCC	$ 1,765.5	€ 90.33	€ 268.63	€ 260.60	£103.06
HCC	$ 522.7	€ 31.30	€ 25.78	€ 15.50	£17.60
LT	$ 161.6	€ 30.09	€ 18.24	€ 15.25	£11.09
PLT	$ 375.7	€ 43.97	€ 8.08	€ 30.35	£4.26

Table 6: Annual predicted economic burden of NAFLD by age group (USA).

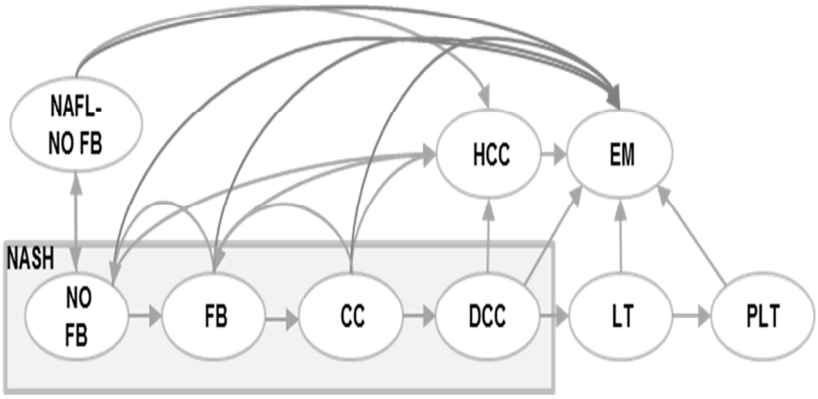
	<20	20-44	45-64	65+	TOTAL
NAFL	$6,841,401,823	$23,039,289,218	$29,801,863,789	$26,881,657,347	$86,564,212,177
NASH NO FB	$126,958,286	$912,550,127	$1,817,290,905	$2,626,815,852	$5,483,615,170
NASH FB	$8,870,534	$160,225,586	$509,199,853	$1,187,975,167	$1,866,271,140
NASH CC	$5,619,143	$233,670,860	$1,300,693,170	$5,033,356,010	$6,573,339,184
NASH DCC	$648,579	$46,701,365	$273,374,952	$1,444,731,427	$1,765,456,323
HCC	$3,018,245	$31,825,298	$111,361,634	$376,535,528	$522,740,705
LT	$250,067	$10,649,057	$75,704,904	$74,963,698	$161,567,727
PLT	$140,478	$13,263,915	$105,324,890	$256,921,848	$375,651,130
TOTAL	$6,986,907,154	$24,448,175,427	$33,994,814,097	$37,882,956,876	$103,312,853,554

Figure 1: General model structure



108x60mm (300 x 300 DPI)

Figure 2: Disease model structure



NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant

108x60mm (300 x 300 DPI)

Figure 3: Comparison of predicted prevalence vs. DISMOD

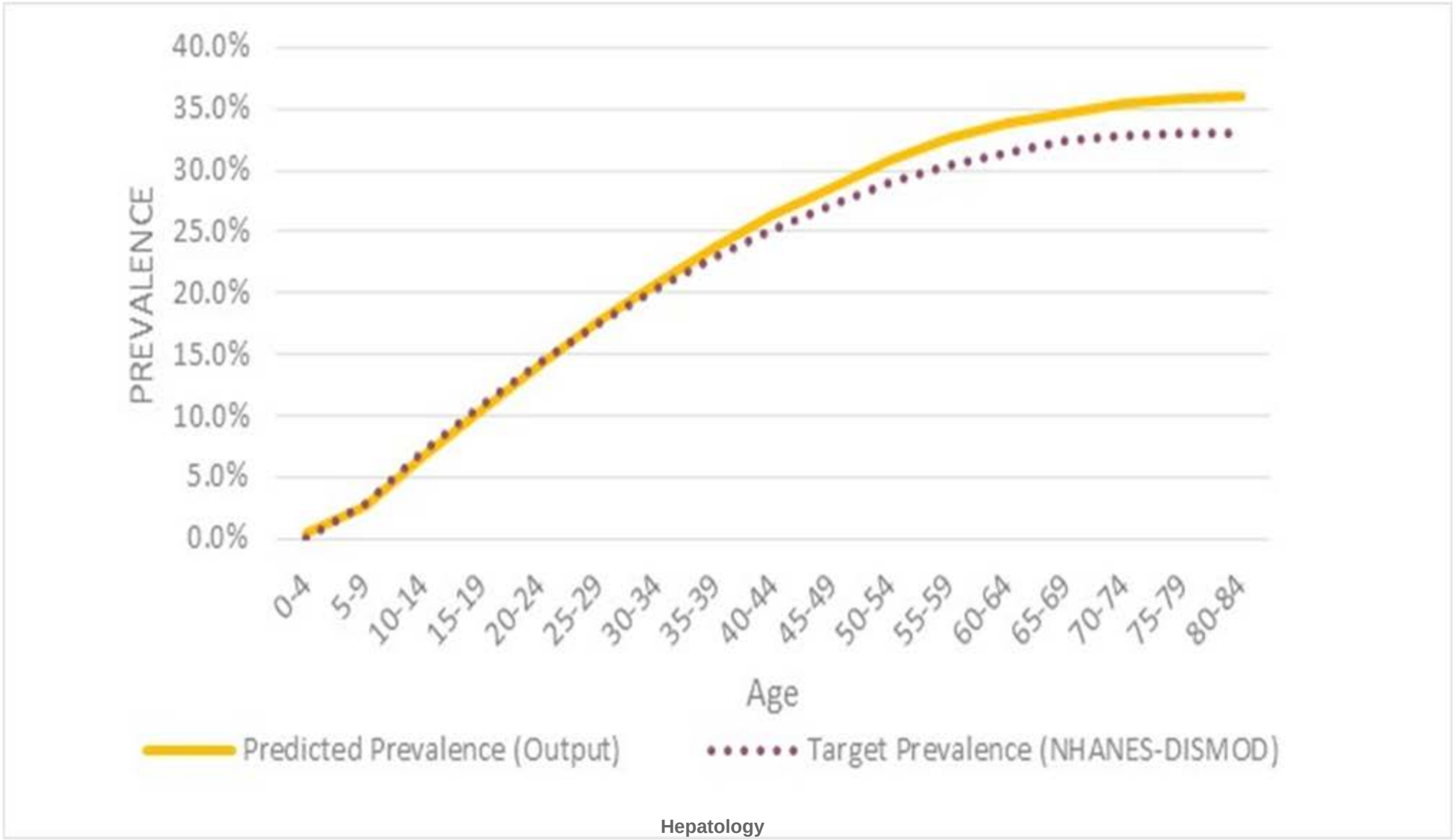
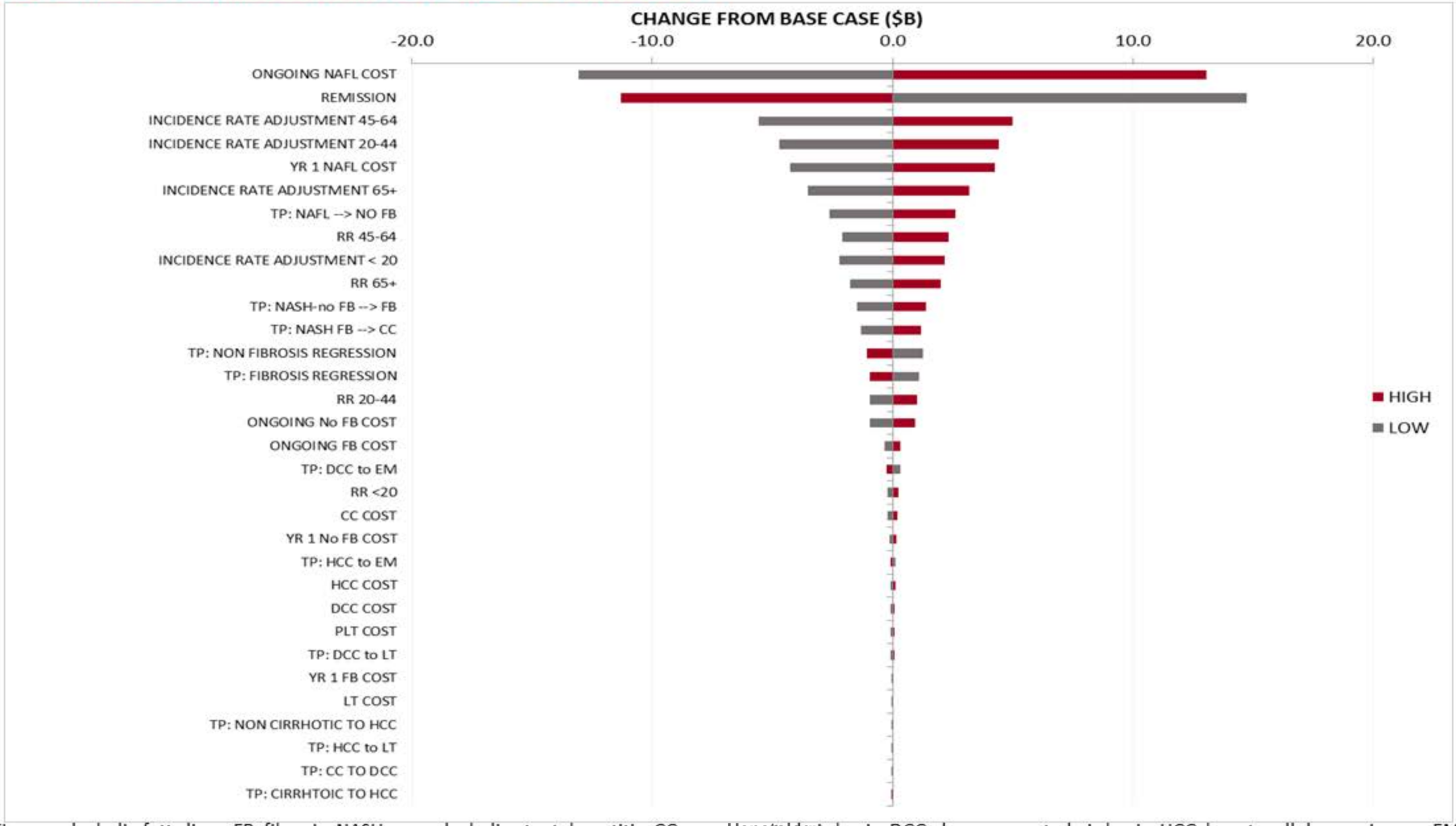


Figure 4: Deterministic Sensitivity Analysis Results (USA)



NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant

Supplementary table 1: Population inputs

		2016 POPULATION[21]					
		USA	GER	FRA	ESP	ITA	UK
0-4	M	10,130,271	1,741,023	2,132,048	1,283,824	1,434,670	1,974,699
5-9	M	10,478,973	1,757,998	2,121,445	1,310,199	1,467,404	1,924,165
10-14	M	10,538,433	1,887,504	2,084,384	1,197,758	1,438,869	1,762,027
15-19	M	10,779,114	2,055,493	2,004,846	1,125,040	1,463,686	1,930,758
20-24	M	11,654,921	2,312,220	2,013,198	1,245,249	1,582,516	2,186,101
25-29	M	11,028,223	2,536,400	2,044,549	1,462,959	1,670,037	2,261,985
30-34	M	10,718,895	2,488,384	2,086,550	1,811,117	1,888,187	2,158,222
35-39	M	9,841,390	2,352,896	2,022,211	2,163,672	2,246,244	1,972,728
40-44	M	10,270,332	2,730,247	2,317,212	2,108,807	2,509,807	2,235,802
45-49	M	10,570,707	3,530,808	2,225,393	1,921,455	2,510,862	2,416,548
50-54	M	11,060,907	3,477,611	2,155,363	1,690,441	2,281,961	2,254,446
55-59	M	10,355,888	2,920,875	2,041,044	1,442,831	1,952,317	1,926,585
60-64	M	8,770,233	2,542,346	1,971,570	1,219,224	1,751,012	1,694,525
65-69	M	7,080,496	1,954,974	1,721,744	1,103,983	1,641,067	1,695,467
70-74	M	4,990,696	2,139,074	1,144,558	859,702	1,372,516	1,207,486
75-79	M	3,448,109	1,748,834	978,960	688,616	1,133,677	927,622
80-84	M	2,374,938	1,625,670	1,352,257	930,342	1,400,787	1,159,449
0-4	F	9,689,758	1,651,040	2,037,181	1,208,249	1,360,340	1,878,437
5-9	F	10,034,435	1,666,438	2,026,834	1,235,372	1,400,595	1,831,155
10-14	F	10,088,520	1,789,858	1,989,170	1,131,536	1,393,612	1,670,856
15-19	F	10,260,586	1,960,081	1,909,830	1,058,827	1,442,996	1,842,889
20-24	F	11,083,094	2,228,485	1,927,361	1,153,684	1,585,194	2,102,257
25-29	F	10,665,583	2,455,989	1,973,298	1,336,907	1,711,693	2,173,790
30-34	F	10,608,568	2,444,134	2,018,599	1,682,975	1,935,423	2,046,860
35-39	F	9,865,249	2,307,919	1,963,340	2,068,303	2,295,324	1,862,364
40-44	F	10,401,851	2,665,016	2,272,339	2,047,574	2,539,642	2,120,914
45-49	F	10,813,204	3,404,800	2,251,928	1,902,330	2,564,303	2,357,876
50-54	F	11,472,872	3,387,137	2,239,569	1,714,108	2,359,427	2,282,133
55-59	F	10,977,155	2,919,144	2,171,273	1,498,960	2,057,266	1,934,839
60-64	F	9,557,556	2,655,022	2,119,351	1,300,419	1,884,995	1,767,878
65-69	F	7,879,512	2,092,727	1,873,137	1,237,766	1,817,235	1,818,013
70-74	F	5,843,388	2,443,796	1,305,269	1,021,137	1,614,462	1,353,951
75-79	F	4,343,202	2,215,033	1,261,933	926,617	1,467,662	1,119,806
80-84	F	3,385,112	2,907,709	2,501,268	1,647,958	2,504,334	1,890,344
		ANNUAL BACKGROUND MORTALITY PROBABILITY [21]					
		USA	GER	FRA	ESP	ITA	UK
0-4	M	0.00029	0.000869	0.000739	0.0006224	0.000676	0.000814
5-9	M	0.00013	0.000099	0.000072	0.000065	0.000067	0.000071
10-14	M	0.00016	0.00008	0.000072	0.000085	0.000081	0.000086
15-19	M	0.00062	0.000315	0.000145	0.000114	0.000134	0.000156
20-24	M	0.00121	0.000448	0.000192	0.000159	0.000157	0.000209
25-29	M	0.00137	0.000535	0.000271	0.000165	0.000188	0.00029
30-34	M	0.00154	0.000696	0.000336	0.000254	0.000267	0.000452
35-39	M	0.00179	0.000956	0.000585	0.000392	0.000433	0.000676
40-44	M	0.00246	0.001517	0.000965	0.000715	0.000719	0.001061
45-49	M	0.00384	0.002676	0.001595	0.001227	0.001256	0.001598
50-54	M	0.00609	0.00476	0.002467	0.001912	0.001976	0.002555
55-59	M	0.00918	0.007928	0.003576	0.002886	0.003043	0.00406
60-64	M	0.01296	0.012158	0.004962	0.004043	0.004729	0.006273
65-69	M	0.01815	0.018177	0.006802	0.005946	0.007534	0.00975
70-74	M	0.02769	0.027332	0.010519	0.010046	0.012392	0.016475

75-79	M	0.0433	0.044515	0.018301	0.019861	0.023432	0.028866
80-84	M	0.07149	0.082758	0.03632	0.041153	0.047526	0.054069
0-4	F	0.00022	0.000708	0.000884	0.0007202	0.000751	0.000999
5-9	F	0.0001	0.000077	0.00009	0.000084	0.000074	0.000085
10-14	F	0.00012	0.00008	0.000095	0.000093	0.000095	0.000104
15-19	F	0.00026	0.000169	0.000312	0.000203	0.000309	0.000319
20-24	F	0.00044	0.000199	0.000593	0.000372	0.000479	0.00048
25-29	F	0.00057	0.000241	0.000735	0.000379	0.000513	0.000628
30-34	F	0.00076	0.000346	0.000894	0.000526	0.000586	0.000841
35-39	F	0.00105	0.000533	0.001179	0.00064	0.000804	0.001235
40-44	F	0.00155	0.000882	0.001759	0.001229	0.001224	0.001806
45-49	F	0.00244	0.001505	0.003033	0.002362	0.002033	0.00257
50-54	F	0.00378	0.002611	0.004863	0.003985	0.003362	0.003791
55-59	F	0.00543	0.004122	0.0078	0.006356	0.005459	0.006084
60-64	F	0.00772	0.006285	0.01137	0.00981	0.009009	0.009755
65-69	F	0.01183	0.009708	0.015146	0.014602	0.0145	0.014797
70-74	F	0.01881	0.014699	0.021726	0.022417	0.02338	0.024932
75-79	F	0.03069	0.026701	0.034275	0.038664	0.04094	0.041521

Supplementary table 2: Non-calibrated disease model transition probability inputs

	NON-CALIBRATED VALUE	SOURCE
NAFL to:		
NASH no FB	0.98%	Ekstedt 2006[22]
HCC	0.04%	Younossi et al 2015[1]
NASH NO FB to:		
NASH FB	5.23%	Younossi et al 2015[1]; Starley et al 2010[23]; Singh et al 2015[42]
HCC	0.04%	Younossi et al 2015[1]
NAFL	5.23%	Starley et al 2010[23]; Singh et al 2015[24]
NASH FB to:		
NASH-CC	5.23%	Younossi et al 2015[1]; Starley et al 2010[23]; Singh et al 2015[24]
HCC	0.04%	Younossi et al 2015[1]
NASH NO FB	5.93%	Starley et al 2010[23]; Singh et al 2015[24]
NASH CC to:		
HCC	2.6%	Assumption based on Ascha 2010[25]
NASH-DCC	3.9%	Dienstag 2011[26]
NASH-FB	5.93%	Starley et al 2010[23]
NASH DCC to:		
HCC	2.6%	Ascha 2010[25]
LT	3.1%	Bennett 1997[27]
EM	12.9%	Fattovich 1997[28]
HCC to:		
EM	62.0%	Younossi et al 2015b[29]
LT	3.1%	Assume the same as for DCC
LT to:		
EM	12.0%	UNOS[30]
PLT	88.0%	UNOS[30]
PLT to:		
EM	3.9%	UNOS[30]

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant; HR, hazard ratio; RR, relative risk

Supplementary Table 3: Transition probability relative risk adjustments by age

AGE	0-19	20-44	45—64	65+	SOURCE
Disease progression	0.48	0.73	0.97	1.21	UNOS[30]
Extra mortality	1.0	1.27	1.10	1.0	NHANES[31]
HCC to LT	1.0	1.0	1.3	0.23	UNOS[31]

Supplementary table 4: Health state costs (year 1 / year 2+)

	USA	GER	FRA	ITA	UK	Sources
NAFL	$1,704 / $1,418	€ 355 / €304	€ 811/ €670	€ 1,273 / €997	£376 / £313	*
NASH-No FB	$2,053 / $1,418	€ 532 / €304	€ 2,401 / €670	€ 2,046 / €997	£529 / £313	*
NASH-FB	$1,418	€ 304	€ 670	€ 997	£ 313	*
NASH-CC	$15,046	€2,988	€6,765	€9,682	£2,812	*
DCC	$24,948	€4,984	€11,251	€16,027	£4,590	*
HCC	$89,387	€22,848	€14,647	€12,803	£10,452	33-38
LT	$181,096	€156,399	€75,997	€91,410	£47,311	33-38
PLT	$44,574	€22,619	€3,256	€17,694	£1,781	33-28

*Microcosted based on expected resource utilization (according to hepatologist consensus) and national fee schedules. Annual costs of hospitalization were based on Sayiner et al (in press)

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant

Supplementary table 5: Utility inputs

Utilities		
NAFL	0.730	Younossi et al 2001[40]
NASH-No FB	0.730	Younossi et al 2001[40]
NASH-FB	0.730	Younossi et al 2001[40]
NASH-CC	0.710	Dan et al 2008[41]
DCC	0.570	Dan et al 2008[41]
HCC	0.496	Assumption based on Hsu 2012[42]
LT	0.567	Younossi et al on file
PLT	0.576	Assumption based on McLernon 2008[33]

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant

Supplementary Table 6: Calibration targets

	MODEL OUTPUT	TARGET	SOURCE
NAFLD Prevalence by age			
<20	5.9%	6.0%	Schwimmer 2008[44]
20-44	16.8%	17.7%	NHANES[31]
45-64	30.2%	33.0%	NHANES[31]
65+	33.3%	32.4%	NHANES[31]
NASH in NAFLD	8.7%	20%	Younossi et al 2015[1], Starley et al 2010[23]
HCC in NAFLD	0.007%	0.0% (0% to 0.07%)	Younossi et al 2015[1], Starley et al 2010[23]

HCC in NASH	0.075%	0.529% (0.08% to 3.8%)	Younossi et al 2015[1], Starley et al 2010[23]
HCC incidence due to NAFLD*	4,166	3,983	SEER[46], Younossi et al 2015b[32]
LT due to NASH	892	906	UNOS[30]

*Calculated based on the SEER-projected incidence of HCC in 2016 multiplied by the percentage of all HCC cases due to NAFLD.

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant; EM, extra mortality

Supplementary table 7: Results: Annual predicted incident cases of disease

	USA	GER	FRA	ITA	UK
NAFL	12,518,147	2,328,210	2,735,859	1,937,422	2,779,771
NASH NO FB	364,048	70,405	86,130	60,668	86,105
NASH FB	155,467	31,929	40,456	28,250	39,655
NASH CC	69,919	15,369	19,462	13,478	18,813
DCC	16,178	3,767	4,862	3,341	4,638
HCC	4,166	931	1,183	817	1,141
LT	892	192	240	167	234

NAFL: non-alcoholic fatty liver; FB, fibrosis; NASH, non-alcoholic steatohepatitis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant

Supplementary table 8: Results: Annual predicted incident cases of disease by age group (USA)

	<20	20-44	45-64	65+
NAFL	1,316,281	3,215,614	4,275,361	3,710,891
NASH NO FB	16,130	62,637	118,586	166,694
NASH FB	1,656	14,534	42,484	96,793
NASH CC	119	2,669	15,299	51,832
NASH DCC	11	533	2,970	12,665
HCC	24	296	933	2,913
LT	1	59	418	414