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Appendix 1

Nonalcoholic fatty liver disease burden – Switzerland 2018–2030

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Additional information

Model description

The model was built in Microsoft Excel® (Microsoft Corp., Redmond, WA) to track the non-alcoholic fatty liver disease (NAFLD) population by fibrosis stage and nonalcoholic steatohepatitis (NASH) status (steatosis only [NAFL] or NASH) from 1950–2030. The relative impact of incident NAFLD cases occurring prior to 1950 was negligible and not included in the analysis. Beginning with estimated annual new NAFLD cases (defined as the onset of steatosis rather than newly diagnosed), fibrosis progression of all cases was modelled up to 2030. Cases by stage of disease were calculated annually by age and gender, with one-year age cohorts to age 84 and cases aged ≥85 years tracked as a single cohort. The population in each age group (excluding the cohort aged ≥85 years) was advanced to the next age to simulate the impact of aging.

Progression of disease through fibrosis and liver disease stages was estimated with adjustment for all-cause mortality (including general background, excess cardiovascular, and liver-related mortality). Fibrosis progression was further adjusted, with overweight individuals (body mass index [BMI] 25 to <30 kg/m^2) having 2.35 greater odds and obese individuals (BMI ≥30 kg/m^2) having 5.70 greater odds of advanced fibrosis, defined as fibrosis stage ≥F3 [1]. It was assumed that the relative differences at the national level in the proportion of overweight and obese individuals would be reflected in each country's NAFLD populations. Incidence of cases by disease stage (*New cases* $_{\text{stage x}}$) were calculated by multiplying progression rates and the total cases at prior stages of the disease in the previous year (*Total Cases* $_{\text{stage x-1, Year Y-1}}$):

$$Total\ Cases_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = \left(Total\ Cases_{Stage_x\ \&\ Year_{y-1}\ \&\ Age\ Cohort_{z-1}}\right) + New\ Cases_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} - All\ Cause\ Mortality_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} - Progressed_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z}$$

where:

$$New\ Cases_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = \left(Total\ Cases_{Stage_{x-1}\ \&\ Year_{y-1}\ \&\ Age\ Cohort_z}\right)\left(Progression\ Rate_{Stage_{x-1} \rightarrow Stage_x\ \&\ Age\ Cohort_z}\right)$$

$$Background\ Mortality_{Stage_x\ \&\ Year_y\ \&\ Age\ Cohort_z} = \left(Total\ Cases_{Stage_x\ \&\ Year_{y-1}\ \&\ Age\ Cohort_z}\right)\left([Background\ Mortality\ Rate][CVD\ Multiplier]_{Age\ Cohort_z}\right)$$

$$Progressed_{Stage_x \,\&\, Year_y \,\&\, Age\ Cohort_z} = (Total\ Cases_{Stage_{x-1} \,\&\, Year_{y-1} \,\&\, Age\ Cohort_z})(Progression\ Rate_{Stage_x \to Stage_{x+1} \,\&\, Age\ Cohort_z})$$

$$Liver\ Related\ Mortality_{Stage_x\ Year_y\ Age\ Cohort_z} = \left(Total\ Cases_{Stage_x\ Year_{y-1}\ Age\ Cohort_{z-1}} - Adjusted\ Background\ Mortality_{Stage_x\ Year_y\ Age\ Cohort_z} - Progressed_{Stage_x\ Year_y\ Age\ Cohort_z}\right)\left(Liver\ Related\ Mortality\ Rate_{Year_{y-1} Age\ Cohort_{z-1}}\right)$$

Age and gender specific fibrosis progression rates were developed and validated based on consensus estimates for the distribution of cases by NASH status and fibrosis stage (fig. S1), and validated using estimates for the incidence of NAFLD-related HCC. Fibrosis progression rates are available from studies reporting highly varied rates, including backward progression (e.g., regression) [2]. In addition, studies are often based on consecutive liver biopsy results, which have a high degree of uncertainty for estimating exact fibrosis stage [3]. For modeling purposes, progression was assumed to be the sum of forward and backward progression.

		Activities
Phase 1 – Data Gathering	1a	**Identify country experts who are willing to collaborate** • Experts were identified through NAFLD-related scientific contributions, or through referrals and recommendations from leading researchers
	1b	**Literature Search** • Review the internal database for previously identified sources • Review online sources (e.g., CDC, etc.) to capture non-indexed sources • Run a literature search to identify recent publications • Summarize input data available through the literature • Gather empirical data for new HCC cases, liver transplants, percent of HCC and transplants due to NAFLD, percent of cases with obesity or DM • Build draft model based on published data • Schedule meeting with experts
Phase 2 – Country Meetings and Modeling	2a	**Expert Meeting 1 (2-3 hours)** • Provide a background on the project, model, and methodology • Review data identified in Phase 1b and highlight gaps in data • Request data in local non-indexed journals, unpublished data, and any other available data (e.g., hospital-level data) that can be used to fill the gaps • Gain agreement on data sources that can used as for extrapolation when no local data are available
	2b	**Follow-up with Experts Post Meeting 1** • Send minutes of the meeting and list of remaining action items to experts • Follow up with experts to collect missing data and get copies of publications, government reports, and unpublished data (e.g., raw hospital or registry-level data) • Analyze raw data and send to experts for approval
	2c	**Disease Burden Modeling** • Populate disease burden model with inputs and calibrate model to empirical data • Schedule second meeting • Develop a slide deck summarizing all inputs and associated data sources • Perform a final check of the model and slide deck and approve internally
	2d	**Expert Meeting 2 (2-3 hours)** • Review all inputs as well as data provided by experts since meeting 1 and results of analyses of any raw data provided • Gain agreement on all inputs to be used in the model • Update the model using any updated inputs
Phase 3 – Follow-up Analyses	3a	**Follow-up Analyses** • Update model as necessary and send results to experts • Provide support to address follow-up questions • Finalize approved inputs and outputs • Update analysis as new information becomes available (e.g., new national studies, updated treatment data)

Figure S1: The Delphi process.

It was assumed that approximately 64% of incident HCC cases would occur among cirrhotics [4]. The remaining 36% of incident HCC cases occurred among F0-F3 cases. The incidence rate among F3 cases

was back-calculated, and progression decreased exponentially with each decreasing level of fibrosis from 0.034% (F3 to HCC) to 0.0004% (F0 to HCC) (table S1). NAFLD-related HCC cases may experience greater mortality as compared to HCV-related HCC; first year mortality (61%) was applied to new HCC cases, with subsequent years' mortality rates based on long-term survival data [5, 6]. A long-term follow-up study of individuals with NASH-related cirrhosis reported that 45% experienced liver failure or decompensated cirrhosis, defined as an increase in Child-Turcotte-Pugh score by 2 points over twelve years of follow-up in patients with Child Class A Cirrhosis [7]. An annual progression rate of 3.71% decompensation among cirrhotics was calculated and applied in the model (table S1).

Table S1: Transition probabilities by disease stage, sex and age group.

Disease stage transition	All cases	Males aged 0–39 years	Males aged ≥40 years	Females aged 0–39 years	Females aged ≥40 years
F0 to F1		0.50%	1.32%	0.42%	1.10%
F1 to F2		3.07%	8.10%	2.56%	6.75%
F2 to F3		3.07%	8.10%	2.56%	6.75%
F3 to Cirrhosis		3.71%	6.05%	3.09%	5.04%
Cirrhosis to DCC	3.71% [7, 16]				
DCC to liver-related death	20.0% [7]				
F0 to HCC	0.0004%				
F1 to HCC	0.0085%				
F2 to HCC	0.017%				
F3 to HCC	0.034%				
Cirrhosis to HCC	0.38%				
HCC to liver related death (year 1)	61.0% [5]				
HCC to liver-related death (subsequent years)	16.20% [6]				

Incidence (new cases) calculation

Recent and accurate estimates of NAFLD incidence and prevalence were either unavailable, had limitations that precluded application to the general population, or were subject to varied diagnostic techniques. Therefore, annual changes in the number of new cases were back calculated using change in adult obesity as a surrogate for the change in new NAFLD cases. In Switzerland, the reported rates of adult obesity have increased over time [8–12]. Long term changes in adult obesity were plotted and trend lines were examined to identify the time period in which the rate of increase was greatest. The growth in NAFLD new cases was assumed to follow the growth in obesity. Future trends in adult obesity was forecasted using best-fit sigmoidal functions. The change in annual prevalence was used to estimate the change in new cases/incidence of adult obesity. The rate of new (incidence) obesity is forecasted to decrease, while total cases (prevalence) will continue to increase.

Total prevalent cases were assumed to be the sum of existing and new NAFLD cases after accounting for mortality and were calibrated to the estimated prevalence of NAFLD in 2015. Incidence was used to describe new NAFLD cases (onset of steatosis) and not the time of first diagnosis. Annual relative incidence values were used to describe changes in the annual number of new NAFLD cases over time based on relative changes in the number of obese adults (BMI ≥30 kg/m^2). A relative incidence curve was fitted from 1950 to the estimated peak of incident adult obesity cases and a second curve followed the decline in relative incidence. The Excel® Solver add-in was used to solve for a constant, which when multiplied by the annual relative incidence resulted in the known prevalence after adjusting for

mortality. This constant multiplied by the relative incidence provided the number of new NAFLD cases per year. Data related to the distribution of NAFL vs. NASH in these populations were used to impute the trends for these histological phenotypes [13–15].

Next, annual incident cases were distributed by age and gender to fit the adjusted NAFLD prevalence. A weighting factor was applied to reported prevalence by age and gender in order to reach estimated NAFLD prevalence in the adult age groups in 2015. The percentage of the incident population allocated to each age and gender cohort in years 1950-1965 was set equal to 1966 with each percentage trended linearly in 5 five-year increments until 2015, at which point the percent of incident cases allocated to each age and gender cohort were held constant until 2030.

Supplementary figure and tables

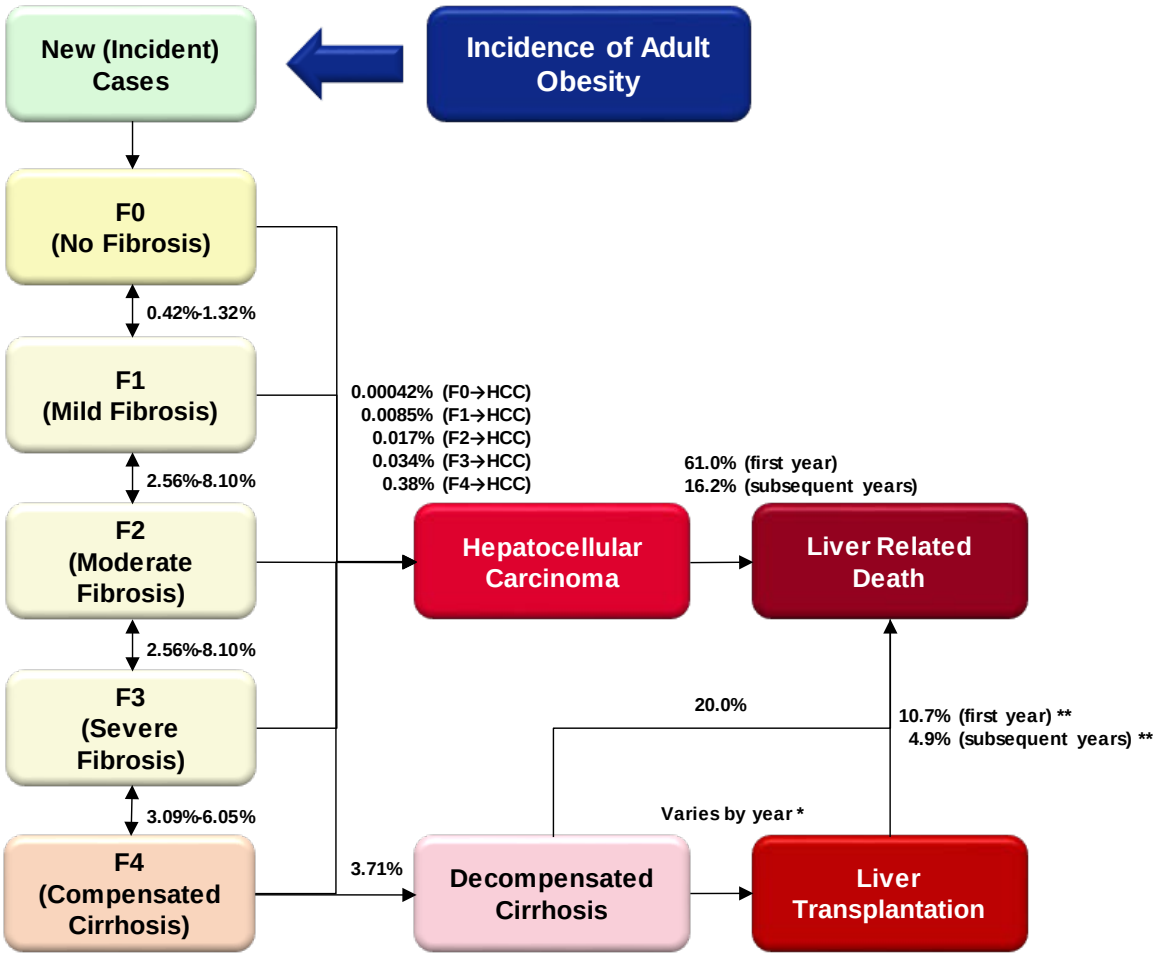

Figure S2: NAFLD disease progression model.

* Transition from decompensated cirrhosis to liver transplantation was calculated annually based on the number of liver transplants and the proportion of liver transplants that were NAFLD-related
** Rates from liver transplantation to liver-related death were applied from 2007–2030. Historical rates were based on estimated survival which has increased over time

Table S2: Mean annual background mortality rates (excluding excess non-liver background and liver deaths), Switzerland 1950–2030.								
Age cohort - males	**1950–1959**	**1960–1969**	**1970–1979**	**1980–1989**	**1990–1999**	**2000–2009**	**2010–2019**	**2020–2029**
0–4	0.727%	0.549%	0.322%	0.213%	0.148%	0.111%	0.089%	0.065%
5–9	0.072%	0.061%	0.049%	0.027%	0.019%	0.011%	0.007%	0.005%
10–14	0.060%	0.047%	0.042%	0.030%	0.020%	0.013%	0.008%	0.006%
15–19	0.118%	0.106%	0.112%	0.097%	0.073%	0.049%	0.032%	0.025%
20–24	0.179%	0.151%	0.169%	0.163%	0.140%	0.078%	0.041%	0.032%
25–29	0.171%	0.138%	0.126%	0.142%	0.136%	0.076%	0.045%	0.036%
30–34	0.187%	0.154%	0.127%	0.128%	0.145%	0.078%	0.051%	0.041%
35–39	0.239%	0.202%	0.166%	0.156%	0.151%	0.105%	0.067%	0.054%
40–44	0.353%	0.312%	0.266%	0.225%	0.214%	0.148%	0.110%	0.089%
45–49	0.568%	0.506%	0.440%	0.357%	0.314%	0.239%	0.173%	0.140%
50–54	0.947%	0.841%	0.736%	0.603%	0.485%	0.390%	0.295%	0.242%
55–59	1.516%	1.418%	1.197%	1.041%	0.793%	0.625%	0.488%	0.403%
60–64	2.369%	2.294%	1.959%	1.679%	1.312%	0.984%	0.782%	0.640%
65–69	3.756%	3.674%	3.229%	2.725%	2.182%	1.575%	1.245%	1.011%
70–74	5.929%	5.732%	5.081%	4.303%	3.559%	2.592%	1.925%	1.552%
75–79	9.600%	9.080%	8.026%	6.912%	5.850%	4.434%	3.360%	2.722%
80–84	15.153%	14.249%	12.813%	11.314%	9.899%	7.907%	6.358%	5.335%
85+	26.652%	25.192%	22.851%	21.404%	20.160%	18.056%	16.911%	15.753%
Age cohort - females	**1950–1959**	**1960–1969**	**1970–1979**	**1980–1989**	**1990–1999**	**2000–2009**	**2010–2019**	**2020–2029**
0–4	0.559%	0.420%	0.236%	0.164%	0.118%	0.093%	0.078%	0.059%
5–9	0.048%	0.038%	0.033%	0.019%	0.013%	0.009%	0.006%	0.005%
10–14	0.036%	0.026%	0.023%	0.017%	0.014%	0.010%	0.007%	0.006%
15–19	0.050%	0.040%	0.044%	0.039%	0.031%	0.022%	0.013%	0.011%
20–24	0.065%	0.050%	0.047%	0.052%	0.041%	0.026%	0.016%	0.013%
25–29	0.088%	0.060%	0.049%	0.052%	0.047%	0.030%	0.021%	0.017%
30–34	0.118%	0.075%	0.065%	0.059%	0.061%	0.039%	0.028%	0.023%
35–39	0.157%	0.115%	0.093%	0.081%	0.075%	0.054%	0.039%	0.032%
40–44	0.232%	0.179%	0.146%	0.126%	0.114%	0.085%	0.065%	0.054%
45–49	0.367%	0.285%	0.242%	0.201%	0.176%	0.143%	0.110%	0.091%
50–54	0.569%	0.452%	0.384%	0.302%	0.276%	0.224%	0.180%	0.151%
55–59	0.887%	0.709%	0.576%	0.470%	0.399%	0.354%	0.293%	0.247%
60–64	1.449%	1.177%	0.908%	0.728%	0.609%	0.529%	0.448%	0.373%
65–69	2.477%	2.033%	1.539%	1.198%	0.992%	0.809%	0.705%	0.584%
70–74	4.330%	3.612%	2.774%	2.098%	1.697%	1.363%	1.123%	0.924%
75–79	7.657%	6.593%	5.139%	3.896%	3.120%	2.477%	2.008%	1.657%
80–84	12.911%	11.584%	9.305%	7.480%	6.049%	4.975%	4.203%	3.579%
85+	23.631%	22.459%	19.787%	17.641%	16.478%	15.052%	14.287%	13.523%

Table S3: Mean annual excess non-liver background mortality rates (excluding liver deaths), Switzerland 1950–2030.								
Age cohort - males	**1950–1959**	**1960–1969**	**1970–1979**	**1980–1989**	**1990–1999**	**2000–2009**	**2010–2019**	**2020–2029**
0–4	0.109%	0.082%	0.048%	0.032%	0.022%	0.017%	0.013%	0.010%
5–9	0.011%	0.009%	0.007%	0.004%	0.003%	0.002%	0.001%	0.001%
10–14	0.009%	0.007%	0.006%	0.005%	0.003%	0.002%	0.001%	0.001%
15–19	0.018%	0.016%	0.017%	0.014%	0.011%	0.007%	0.005%	0.004%
20–24	0.027%	0.023%	0.025%	0.024%	0.021%	0.012%	0.006%	0.005%
25–29	0.026%	0.021%	0.019%	0.021%	0.020%	0.011%	0.007%	0.005%
30–34	0.028%	0.023%	0.019%	0.019%	0.022%	0.012%	0.008%	0.006%
35–39	0.036%	0.030%	0.025%	0.023%	0.023%	0.016%	0.010%	0.008%
40–44	0.053%	0.047%	0.040%	0.034%	0.032%	0.022%	0.016%	0.013%
45–49	0.085%	0.076%	0.066%	0.054%	0.047%	0.036%	0.026%	0.021%
50–54	0.142%	0.126%	0.110%	0.090%	0.073%	0.058%	0.044%	0.036%
55–59	0.227%	0.213%	0.179%	0.156%	0.119%	0.094%	0.073%	0.060%
60–64	0.355%	0.344%	0.294%	0.252%	0.197%	0.148%	0.117%	0.096%
65–69	0.563%	0.551%	0.484%	0.409%	0.327%	0.236%	0.187%	0.152%
70–74	0.889%	0.860%	0.762%	0.646%	0.534%	0.389%	0.289%	0.233%
75–79	1.440%	1.362%	1.204%	1.037%	0.877%	0.665%	0.504%	0.408%
80–84	2.273%	2.137%	1.922%	1.697%	1.485%	1.186%	0.954%	0.800%
85+	3.998%	3.779%	3.428%	3.211%	3.024%	2.708%	2.537%	2.363%
Age cohort - females	**1950–1959**	**1960–1969**	**1970–1979**	**1980–1989**	**1990–1999**	**2000–2009**	**2010–2019**	**2020–2029**
0–4	0.084%	0.063%	0.035%	0.025%	0.018%	0.014%	0.012%	0.009%
5–9	0.007%	0.006%	0.005%	0.003%	0.002%	0.001%	0.001%	0.001%
10–14	0.005%	0.004%	0.003%	0.003%	0.002%	0.001%	0.001%	0.001%
15–19	0.007%	0.006%	0.007%	0.006%	0.005%	0.003%	0.002%	0.002%
20–24	0.010%	0.007%	0.007%	0.008%	0.006%	0.004%	0.002%	0.002%
25–29	0.013%	0.009%	0.007%	0.008%	0.007%	0.005%	0.003%	0.003%
30–34	0.018%	0.011%	0.010%	0.009%	0.009%	0.006%	0.004%	0.003%
35–39	0.024%	0.017%	0.014%	0.012%	0.011%	0.008%	0.006%	0.005%
40–44	0.035%	0.027%	0.022%	0.019%	0.017%	0.013%	0.010%	0.008%
45–49	0.055%	0.043%	0.036%	0.030%	0.026%	0.022%	0.016%	0.014%
50–54	0.085%	0.068%	0.058%	0.045%	0.041%	0.034%	0.027%	0.023%
55–59	0.133%	0.106%	0.086%	0.071%	0.060%	0.053%	0.044%	0.037%
60–64	0.217%	0.177%	0.136%	0.109%	0.091%	0.079%	0.067%	0.056%
65–69	0.372%	0.305%	0.231%	0.180%	0.149%	0.121%	0.106%	0.088%
70–74	0.649%	0.542%	0.416%	0.315%	0.254%	0.204%	0.168%	0.139%
75–79	1.149%	0.989%	0.771%	0.584%	0.468%	0.371%	0.301%	0.249%
80–84	1.937%	1.738%	1.396%	1.122%	0.907%	0.746%	0.630%	0.537%
85+	3.545%	3.369%	2.968%	2.646%	2.472%	2.258%	2.143%	2.028%

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