Appendix 1 (as supplied by the authors): Supplemental material

Supplemental Table S1. Delphi Process

		Activities
Phase 1 – Data Gathering	1a	Identify area 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 hepatocellular carcinoma cases, liver transplants, percent of hepatocellular carcinoma and transplants due to NAFLD, percent of cases with obesity • Build draft model based on published data • Schedule meeting with experts
Phase 2 – Area 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• Review data identified in Phase 1b and highlight gaps in data • Request data in local non-indexed journals, unpublished data and any other available data (e.g., hospital-level data) that can be used to fill the gaps • Gain agreement on data sources that can used as for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to experts • Follow up with experts to collect missing data and get copies of publications, government reports and unpublished data (e.g., raw hospital or registry-level data) • Analyze raw data and send to experts for approval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)

Appendix to: Swain MG, Ramji A, Patel K, et al. Burden of nonalcoholic fatty liver disease in Canada, 2019–2030: a modelling study. *CMAJ Open* 2020. DOI:10.9778/cmajo.20190212.

Supplemental Table S2. Data Sources

Model Input		Value	Data source
Population		Varied by year, gender and age group	(1)
Background Mortality		Varied by year, gender and age group	(1)
Background Mortality: Standard Mortality Ratio (excess non-liver mortality)	Base Low High	1.42-1.43 (F3/F4 cases aged ≤75 years) 1.00 (all stages) 1.80 (excluding simple steatosis cases)	(2, 3) No adjustment (4)
Adult Obesity Prevalence		See Figure 2	(5-8)
Total Transplants		Varied by year	(9, 10)
Transplants: NAFLD-Related		25%	Expert consensus
NAFLD Prevalence (ages ≥20 years in 2018)	Base Low High	25.0% 22.5% 27.5%	Expert consensus
NAFLD Prevalence: Distribution by Age and Gender		See Figure S3	(11-14)

Compared to Model Projections for Hepatocellular Carcinoma Incidence		Value	Data source
Liver Cancer Incidence (2010)		1,845	(15)
Morphology: Hepatocellular Carcinoma		72%	(16)
Etiology: NAFLD-Related Hepatocellular Carcinoma	High Low	4.0% 34.8%	(17, 18)

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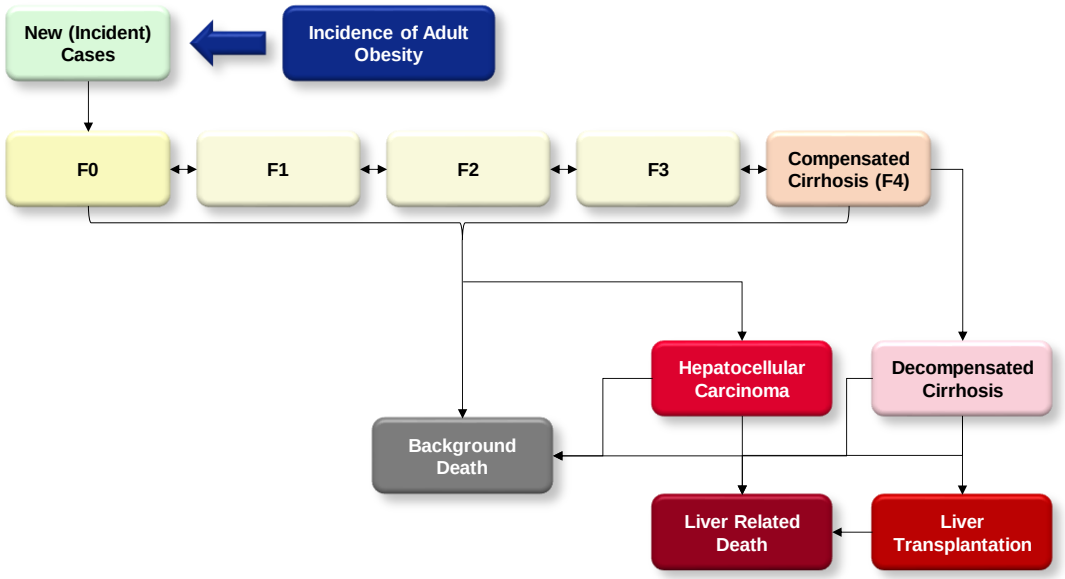
Supplemental Figure S1. NAFLD Disease Progression Model



Appendix to: Swain MG, Ramji A, Patel K, et al. Burden of nonalcoholic fatty liver disease in Canada, 2019–2030: a modelling study. *CMAJ Open* 2020. DOI:10.9778/cmajo.20190212.

Model Description: The nonalcoholic fatty liver disease (NAFLD) Markov model (Figure 1) was designed using Microsoft Excel® 2010 (Microsoft Corp., Redmond, WA) to track the NAFLD population by fibrosis stage as well as nonalcoholic steatohepatitis (NASH) status from 1950-2050. The relative impact of incident NAFLD cases occurring prior to 1950 was negligible and was not included in the analysis. Model generated uncertainty intervals (UI) were calculated using high/low Beta-PERT distributions around inputs and conducting Monte Carlo analysis using Oracle Crystal Ball® (Oracle Corp., Redwood City, CA, Release 11.1.3708.0).

Beginning with the estimated annual new NAFLD cases (defined as the onset of steatosis rather than newly diagnosed), fibrosis progression of all cases was modeled through 2030. Cases by stage of disease were calculated annually by age and gender, with one-year age cohorts through age 84 and cases aged ≥85 years tracked as a single cohort. Annually, the population in each age group (excluding the ≥85 year cohort) was advanced to the next age to simulate the impact of aging. Historical and medium-fertility projection population data for all countries were obtained from the United Nations' population database by gender and one year age cohort (1).

Disease progression was simulated by multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage. Age specific fibrosis progression rates were back-calculated based on assumptions for the distribution of cases by NASH status and fibrosis stage (described below). For the purpose of the model, progression rates were assumed to be the sum of forward progression minus the rate of regression, which is common among NAFLD cases based on studies of consecutive liver biopsies (19).

Disease progression through fibrosis and advanced liver disease (decompensated cirrhosis and hepatocellular carcinoma) (Figure 1) was estimated with adjustment for all-cause mortality (including general background, excess cardiovascular and liver-related mortality). New 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 ($Total\ Cases_{\text{stage x-1, Year Y-1}}$) as shown in Equation 1.

Equation 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:

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

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

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

$$\text{Liver Related Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_x\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}} - \text{Adjusted Background Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Progressed}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z}\right)\left(\text{Liver Related Mortality Rate}_{\text{Year}_{y-1}\text{Age Cohort}_{z-1}}\right)$$

Transition Rates: The annual transition probabilities were based on published estimates and expert consensus and back-calculated (Table 3). Age and gender specific fibrosis progression rates were developed based on assumptions for the distribution of cases by NASH status and fibrosis stage, as described below. Fibrosis progression rates are available from studies analyzing consecutive liver biopsies, but report highly varied rates, including negative progression (e.g. regression) (19). For the purpose of the model, progression rates were assumed to be the sum of forward progression minus the rate of regression. Where data or expert input were available for the incidence of NAFLD-related hepatocellular carcinoma, decompensated cirrhosis and related mortality, progression rates were modified to align with reported data and expert consensus.

During initial model development, rates of development of hepatocellular carcinoma in the US model were calibrated to national data from the Surveillance, Epidemiology, and End Results Program (SEER) for liver and intrahepatic bile duct cancer incidence (20). It was conservatively assumed that 72% of all liver cancers were hepatocellular carcinoma (21). In addition, it was assumed that 12.6-14.8% of modeled

incident hepatocellular carcinoma cases during 2004-2009 were attributable to NAFLD/NASH based on a study of SEER and Medicare-linked data for 4,929 hepatocellular carcinoma cases during the same time period (22). It was assumed that 64% of incident hepatocellular carcinoma cases would occur among cirrhotics (23). The annual transition rate from F4 to hepatocellular carcinoma was estimated at 0.48%. The remaining 36% of incident hepatocellular carcinoma 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 0.044% (F3 to hepatocellular carcinoma) to 0.00054% (F0 to hepatocellular carcinoma). NAFLD-related hepatocellular carcinoma cases may experience greater mortality as compared to HCV-related hepatocellular carcinoma; first year mortality (61%) was applied to new hepatocellular carcinoma cases, with subsequent years mortality rates based on long-term survival data (22, 24). 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 (25). An annual progression rate of 3.8% decompensation among cirrhotics was calculated and applied in the model.

NASH diagnosis traditionally relies upon liver biopsy results, which are subject to observer and sampling variability (26), and patient selection bias, as NASH may also be detected by histology in NAFLD cases with normal liver enzyme levels (27). Prevalent NASH cases were based on the estimated distribution of fibrosis cases among the total NAFLD population, with increasing fibrosis associated with higher likelihood of NASH. Because NASH can remit in NAFLD patients, and fibrosis can regress (19, 28), an assumption was applied in the model where a small portion of NAFLD cases were assumed to have previously experienced NASH with subsequent regression, with an exponential decline in likelihood of regressed NASH with each increase in fibrosis stage.

As the NAFLD model was developed, both fibrosis progression rates and the proportion of NASH by fibrosis stage were calibrated to reported data for NASH-related hepatocellular carcinoma (29). Fibrosis progression rates were adjusted for Canada using relative rates of overweight (BMI >25 ≤30 kg/m^2) and obesity (BMI <30kg/m^2) (5) as well as reported risk of progressive disease by BMI class (30), with overweight individuals (BMI 25 to <30kg/m^2) having 2.35 greater odds and obese individuals (BMI

≥30kg/m^2) having 5.70 greater odds of advanced fibrosis (30). Therefore, a larger proportion of advanced fibrosis cases within the model is a result of the increasing age of the population, the relative timing of increases in obesity, and the comparative burden of overweight and obesity.

Supplemental Table S3. Model 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	Data Source
F0 to F1		0.60% (0.35%-0.91%)	1.58% (0.93%-2.41%)	0.50% (0.29%-0.76%)	1.31% (0.77%-2.01%)	Back-calculated
F1 to F2		3.66% (2.16%-5.61%)	9.67% (5.69%-14.81%)	3.05% (1.80%-4.68%)	8.06% (4.74%-12.35%)	Back-calculated
F2 to F3		3.66% (2.16%-5.61%)	9.67% (5.69%-14.81%)	3.05% (1.80%-4.68%)	8.06% (4.74%-12.35%)	Back-calculated
F3 to Compensated Cirrhosis		4.43% (2.53%-8.42%)	7.23% (4.12%-13.74%)	3.69% (2.11%-7.02%)	6.02% (3.44%-11.45%)	Back-calculated
Compensated Cirrhosis to Decompensated Cirrhosis	3.71% (2.60%-5.03%)					(25, 31)
Decompensated Cirrhosis to Liver Related Death	20.0% (16.0%-24.0%)					(25)
F0 to Hepatocellular Carcinoma	0.00054% (0.00040%-0.00071%)					(22, 23)
F1 to Hepatocellular Carcinoma	0.0109% (0.0081%-0.0143%)					(22, 23)
F2 to Hepatocellular Carcinoma	0.022% (0.016%-0.029%)					(22, 23)
F3 to Hepatocellular Carcinoma	0.044% (0.033%-0.058%)					(22, 23)
Cirr to Hepatocellular Carcinoma	0.48% (0.36%-0.63%)					(22, 23)
Hepatocellular Carcinoma to Liver Related Death (Year 1)	61.0% (37.1%-66.4%)					(22)
Hepatocellular Carcinoma to Liver Related Death (Subsequent Years)	16.20% (11.03%-23.06%)					(24)

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Incidence (New Cases) Calculations

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 the change in obesity prevalence as a surrogate for the change in new NAFLD cases. 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 among the population aged ≥20 years in 2018:

$$\text{Total NAFLD Cases (Prevalent Cases)}_{\text{Year}_y} = \sum_{t=1950\text{-}2018}^{y} \left(\text{New NAFLD Cases (Incident Cases)}_t - \text{Mortality}_t\right)$$

Incidence was used to describe new NAFLD cases (onset of steatosis) and not the time of first diagnosis. It was assumed anyone who developed incident NAFLD prior to 1950 is no longer alive. The total number of NAFLD cases in 2018 was applied in the model and the annual number of deaths (mortality) was calculated in the model using liver related and non-liver related deaths. Solving the above equation for new NAFLD cases provides the average number of new NAFLD cases per year. To account for the fact that the number of new NAFLD cases was not constant over time, a relative incidence curve was used.

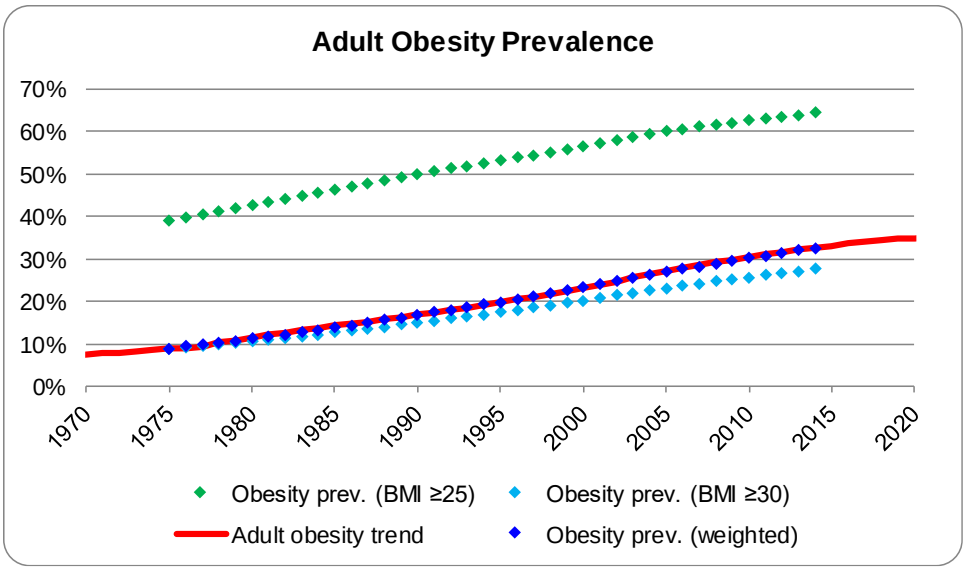
In Canada, the reported rates of adult obesity have increased over time (Figure 2). Long term changes in adult obesity prevalence at two cutoff levels were plotted, and after weighting for the population at each cutoff level, the growth in NAFLD prevalence was assumed to follow the growth in obesity. Future trends in adult obesity were forecasted using best-fit sigmoidal functions. The change in annual prevalence was used to estimate the change in incidence of adult obesity.

Annual relative incidence values were used to describe changes in the annual number of new NAFLD cases over time. The Excel® Solver add-in was used to solve for the 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.

Next, annual incident cases were distributed by age and gender to fit the adjusted NAFLD prevalence, and a weighting factor was applied to reported prevalence by age and gender in order to meet 25%

prevalence among the Canadian population aged ≥20 years in 2018. The percentage of the incident population allocated to each age and gender cohort was trended linearly in 5 five-year increments until 2018, at which point the percent of incident cases allocated to each age and gender cohort were held constant until 2030.

Supplemental Figure S2. Adult Obesity Prevalence – 1970-2020 *



* Based on prevalence of adults at BMI ≥25, BMI ≥30, and BMI adjusted for ethnicity (5-8).

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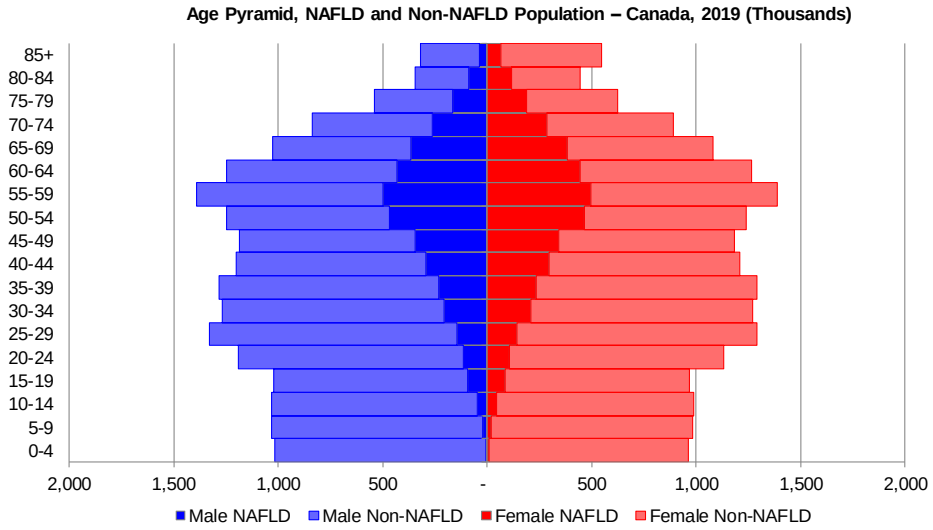
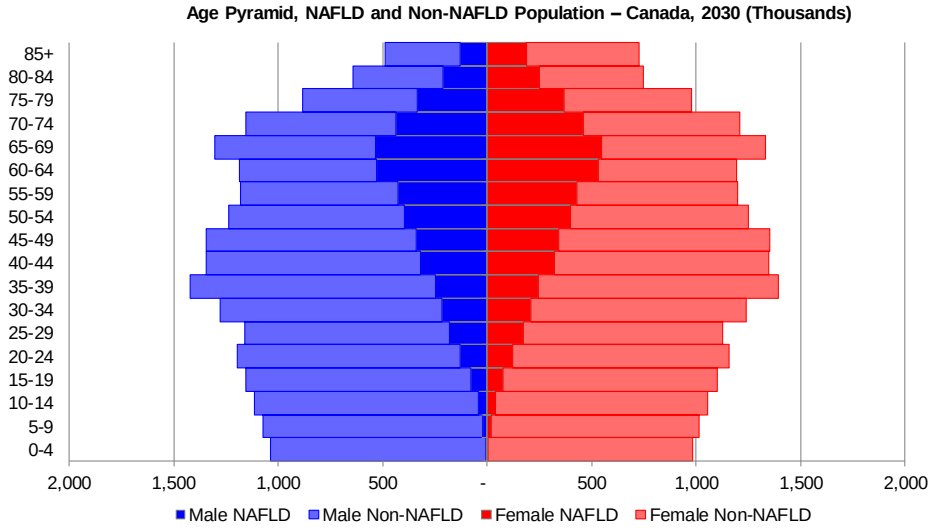
Supplemental Figure S3. Age Distribution of Model-Estimated Prevalent NAFLD Cases – Canada, 2019 & 2030





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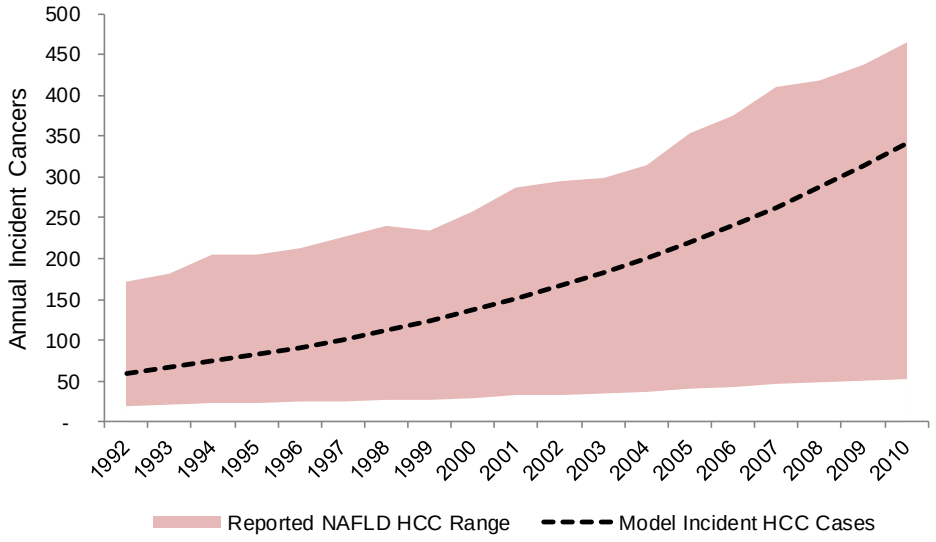
Liver Cancer: Surveillance data for liver cancer were compared to the model outputs for projected incident hepatocellular carcinoma cases. Statistics Canada reports annual incident liver cancer cases for 1992-2010 (15) and an estimated 72% of incident cancers were assumed to be classified as hepatocellular carcinoma (16). A range of 4.0% to 34.8% was considered for the proportion of hepatocellular carcinoma that could be NAFLD-related (17, 18). This range was compared to model predicted incident NAFLD-related hepatocellular carcinoma (Figure 4).

Supplemental Figure S4. Reported Range* of Incident NAFLD-Related Hepatocellular Carcinoma and Model-Estimated Incident Hepatocellular Carcinoma

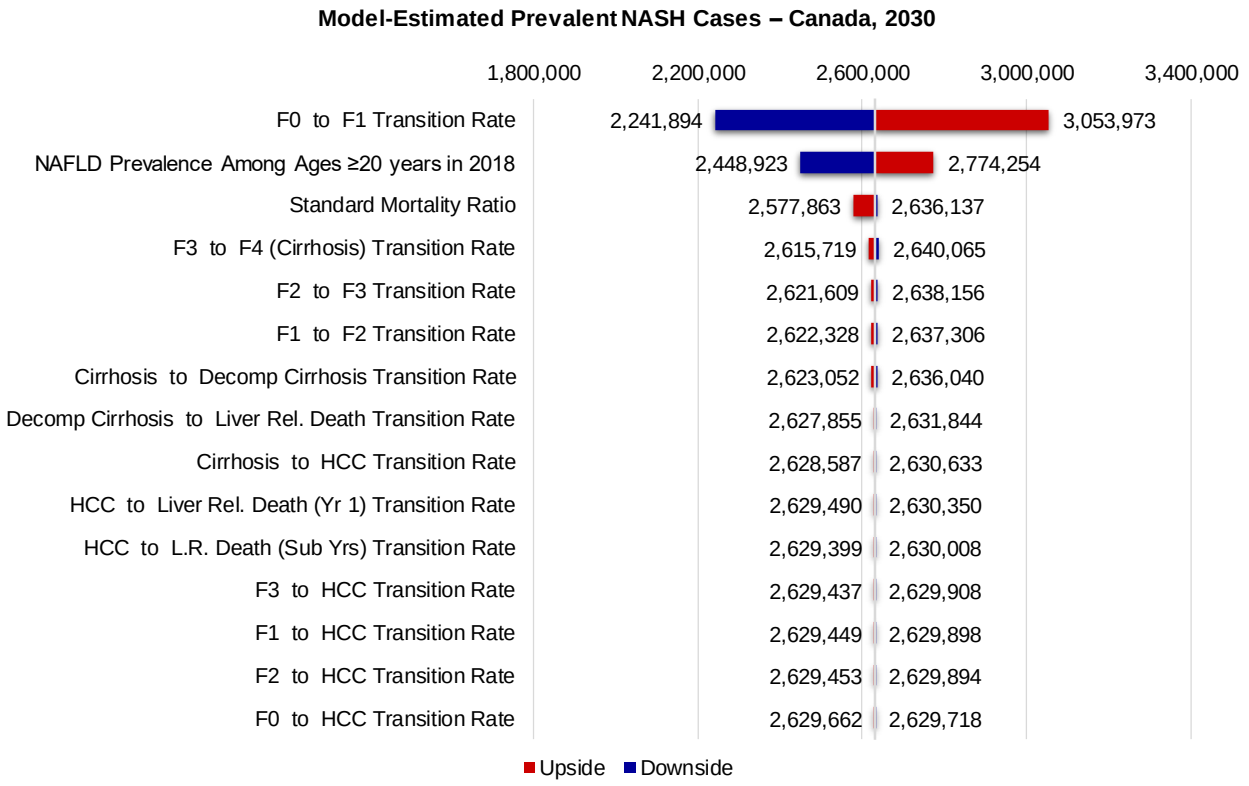


* Reported liver cancer cases (15); 72% of incident cancers assumed to be hepatocellular carcinoma (16); 4.0-34.8% could be NAFLD-related (17, 18)

Uncertainty and Sensitivity Analysis

Uncertainty intervals (UI) were generated using Beta-PERT distributions around key uncertainties by Monte Carlo analysis using Oracle Crystal Ball® (Oracle Corp., Redwood City, CA, Release 11.1.3708.0). Monte Carlo simulation was used to identify model inputs that accounted for the greatest variation in future disease burden, and to produce 95% uncertainty intervals for selected model outputs. Beta-PERT distributions (32) were defined for model inputs for NAFLD prevalence, excess background mortality multipliers, and disease transition probabilities (Table 2 & Table 3). Sensitivity analysis was conducted to identify and quantify key drivers of uncertainty for the number of model projected NASH cases in 2030.

Supplemental Figure S5. Key Drivers of Uncertainty for Model-Estimated Prevalent NASH Cases – Canada, 2030



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