Developing a Population-level Disease Burden Model for NASH in the US: Methodological Challenges and Considerations

Andrew Briggs[1,2], John Schneider[1], Shawn Davies[1], Andrew Lloyd[3], Daniel Aggio[3], Villum Wittrup-Jensen[4], Salvador Augustin[4], Nadine Chami[1]

1. Avalon Health Economics LLC, Miami, Florida, USA. 2. London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London, UK. 3. Acaster Lloyd Consulting Ltd, London, United Kingdom. 4. Boehringer Ingelheim International GmbH, Binger Strasse 17, Ingelheim am Rhein, 55216, Germany.

Poster Code: MSR38

INTRODUCTION

- Although the progression of non-alcoholic steatohepatitis (NASH) has been described in several health economic models, the relationship with the population burden of disease is not well understood.
- In seeking to estimate a US population-level burden of disease model for NASH we confronted several methodological challenges:
  1. the lack of robust incidence data in the literature
  2. the indolent nature of the early disease stages, and
  3. decomposition of the humanistic burden into morbidity and mortality impacts.

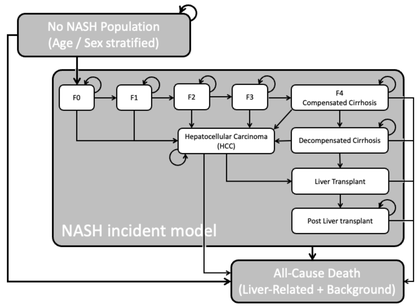
OBJECTIVE

- **Our aim is to describe our approach to meeting these challenges using calibration to estimate incidence of NASH and using a novel method to disaggregate morbidity and mortality elements of burden within a population pyramid presentation of the burden by age and sex**
- **A further aim is to promote the simultaneous use of spreadsheet (Excel™) and script (R) modelling to provide validation and verification while facilitating model sharing**

MODEL

- The population model of NASH is presented in Figure 1 and has been described in detail in the accompanying poster reporting the model results (see poster PCR139)
- Of note is that the incident model for NASH is nested within a wider (and very simple) population without NASH
- A key parameter to be estimated in the incidence of NASH from the no-NASH population

Figure 1. Population model with nested incident NASH model



Note: Model assumes a 'net-effect' of fibrosis progression and regression

ESTIMATING INCIDENCE OF NASH BY AGE 1/2

- Incidence of NASH is unobservable because the F0 state of fibrosis is 'sub-clinical'
- Later (symptomatic) stages of NASH are observable (F4, decompensated cirrhosis, hepatocellular carcinoma) and prevalence estimates appear in the literature
- Calibration is therefore an option given a specified underlying incidence model (Figure 1)

ESTIMATING INCIDENCE OF NASH BY AGE 2/2

- Underlying incidence of NASH is assumed to be a constant
- However, obesity and diabetes are known risk factors for NASH
- Taking an assumed risk ratio for NASH of 10.07 for those with obesity and 1.78 for those with diabetes from the literature [1] we developed an age related incidence for NASH (Table 1)

Table 1. Prevalence of obesity, diabetes and estimated incidence of NASH by age

Age Group	Prevalence Obesity in US [2]	Prevalence Diabetes	Calculated Relative Risk	NASH Incidence Rate
0-5	13.4%	0.25%	1.002	0.02%
6-11	20.3%	0.25%	2.843	0.05%
12-17	21.2%	0.25%	2.925	0.05%
18-19	21.2%	4.2%	2.956	0.05%
20-39	40.0%	4.2%	4.661	0.09%
40-44	40.0%	17.5%	5.096	0.09%
45-59	44.8%	17.5%	5.200	0.10%
60-64	42.8%	17.5%	5.018	0.09%
65+	42.8%	26.8%	5.091	0.09%

- Calibration was then used to get the underlying incidence of NASH by age shown in the final column of Table 1 averaged over the several calibration targets from the literature (shown in Table 2)

Table 2. Calibrating incidence of NASH from prevalence targets

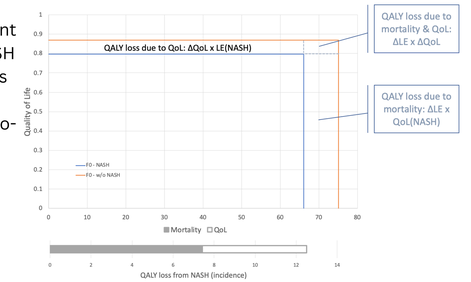
Metric	Target Definition	Reported Value	Source	Calibrated Incidence Rate
Prevalence	F4 and DC	40,973,831	[3]	100%*
Prevalence	HCC	6,447	[3]	0.012%
Prevalence Rate	F0-F4, HCC, DCC, LT, PLT	1.5% - 6.45%	[4]	0.010% - 0.045%
Prevalence Rate	F0-F4, HCC, DCC, LT, PLT	2.67%	[5]	0.023%
Prevalence Rate	F4, DCC (aged 18+)	0.178%	[6]	0.008%
Prevalence Rate	F4, DCC (aged 18+)	0.12%	[7]	0.003%
Prevalence Rate	F0-F4, HCC, DCC, LT, PLT	2.79%	[8]	0.024%

**This target led to implausibly high incidence estimates and was excluded from the Table 1 average*

DISAGGREGATING MORBIDITY & MORTALITY BURDEN

- Quality adjusted life expectancy (QALE) burden is estimated from the model for incident NASH (Figure 1) by comparing incident estimates with QALE estimates in absence of NASH
- Average LE is estimated with & without NASH by not applying quality of life (QoL) weights
- Average QoL is estimated by dividing QALE by LE
- Profiles in Figure 2 show LE on x-axis and average QoL on y-axis for NASH (blue) and no-NASH orange
- Area under each profile is thus quality-adjusted life years (QALY) for NASH & no-NASH
- Area between the profiles represents the burden of NASH
- This area is disaggregated into three areas:
  1. Morbidity contribution to QALY
  2. Mortality contribution to QALY
  3. Area (to the northeast) that is both morbidity and mortality contribution to QALY
- This third area is shared equally between morbidity and mortality to generate the disaggregated burden in terms of QALE

Figure 2. Burden of NASH: individual (lifetime)



ESTIMATING BURDEN OVER THE LIFE-COURSE CONDITIONAL ON AGE AT ONSET

- Our poster presenting the results of the model showed the burden of NASH varies by age and sex depending on age at onset (see poster PCR139)
- Here we show how we can use the model to show how the burden is distributed across the life-course of the individual conditional on age of onset (Figure 3)
- These conditional results can then be combined with the age pyramid of the US population (see poster PCR139) to show the burden across age-sex strata of the US population (Figure 4)
- The 'spinning top' shape of the life-course burden reflects the insidious nature of the disease

Figure 3. Burden of incident NASH over the life course (incidence age 0-9 vs. 40-49 years)

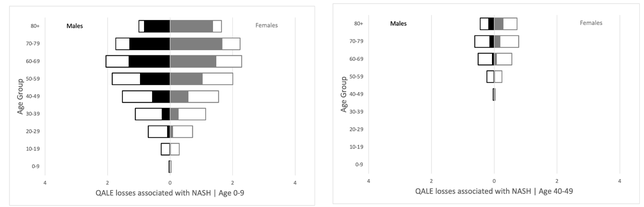
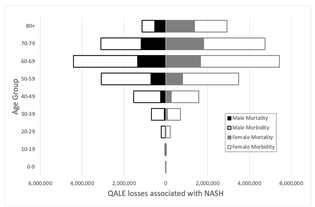


Figure 4. US population life course NASH burden



VALIDATION OF THE MODELLING

- The initial model was programmed in Microsoft Excel™
- The model was subsequently replicated in the script language 'R'
- During this process a number of minor errors in the original model were identified
- Replication using a very different modelling platform (script vs. spreadsheet) offers confidence in the final model
- Two different versions in two different platforms facilitates sharing with a broad range of potential users

DISCUSSION AND CONCLUSIONS

- This poster (MSR38) focusses on the methodological challenges in developing a population level burden of disease model for NASH
- Results are reported in poster PCR139
- Calibration to inform incidence estimates is not frequently done and we focus on the methods employed in this study
- Disaggregation of disease burden is rarely performed and we show a simple and novel approach to doing so
- We also illustrate how disaggregated burden can then be combined into a population pyramid presentation

REFERENCES

1.Eskridge W, et al. PLoS One. 2021;16(11):e0260320.
2. Hales CM, et al. NCHS Data Brief. 2020 Feb;(360):1–8.
3. Zhang T, et al. J Cancer. 2021;12(10):2855–65.
4. Younossi ZM. Clin Liver Dis (Hoboken). 2018 Apr;11(4):92–4.
5.Younossi ZM, et al. Hepatology. 2019 Feb;69(2):564–72.
6. National Diabetes Statistics Report [Internet]. Centers for Disease Control and Prevention. 2022.
7. State Population by Characteristics: 2010-2019 [Internet]. United States Census Bureau. 2021.
8. Kabbany MN, et al. Am J Gastroenterol. 2017 Apr;112(4):581–7

DISCLOSURES

This study was sponsored and funded by Boehringer Ingelheim International GmbH